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MEDDELANDE FRÅN KOMMISSIONEN TILL EUROPAPARLAMENTET, RÅDET, EUROPEISKA EKONOMISKA OCH SOCIALA KOMMITTÉN SAMT REGIONKOMMITTÉN

Reform av läkemedelslagstiftningen och åtgärder mot antimikrobiell resistens

1. Inledning

I över 50 år har EU:s läkemedelslagstiftning fastställt de högsta kvalitets-, säkerhets- och effektivitetsstandarderna för godkännande av läkemedel och samtidigt främjat den inre marknadens funktion och en konkurrenskraftig läkemedelsindustri. De pågående omställningarna tillsammans med erfarenheterna från covid-19-pandemin och Rysslands brutala invasion av Ukraina kräver dock beslutsamma åtgärder för att modernisera EU:s läkemedelsram och göra den mer resilient, rättvis och konkurrenskraftig.

Läkemedel som godkänns i EU i dag når inte patienterna tillräckligt snabbt och är inte lika tillgängliga i alla EU-länder. Det råder stora skillnader när det gäller hanteringen av icke tillgodosedda medicinska behov, sällsynta sjukdomar och utvecklingen av nya antimikrobiella medel för att motverka det växande problemet med antimikrobiell resistens. Dessutom är höga priser för innovativa behandlingar en utmaning när det gäller att säkerställa snabb och prisöverkomlig tillgång till läkemedel, och läkemedelsbrist är också ett växande problem som kan få allvarliga konsekvenser för patienterna.

Om EU ska förbli en attraktiv plats för investeringar och världsledande när det gäller utvecklingen av läkemedel, måste regelverket anpassas till utvecklingen, exempelvis den digitala omställningen och ny teknik för att administrera läkemedel till patienterna. För att öka EU:s konkurrenskraft måste den administrativa bördan minska och förfarandena förenklas, och om detta initiativ ska kunna anpassas efter målen i den europeiska gröna given och den gröna ekonomin är det viktigt att hantera läkemedlens miljöpåverkan.

I november 2020 lade kommissionen fram en läkemedelsstrategi för Europa[1] som syftar till att skapa en framtidssäker och patientcentrerad läkemedelsmiljö där EU:s industri kan verka innovativt, nå framgång och fortsätta att vara världsledande. Ett läkemedelsekosystem i EU som är krisresilient och anpassat till dagens situation och framtida utmaningar är en av de viktigaste pelarna i en stark europeisk hälsounion[2] som fungerar för medborgarna och kommer att komplettera andra viktiga initiativ. Det gäller exempelvis förstärkningen av EU:s ram för hälsosäkerhet genom den nya lagstiftningen om gränsöverskridande hot mot människors hälsa, starkare mandat för EU:s hälso- och sjukvårdsorgan, inrättandet av Myndigheten för beredskap och insatser vid hälsokriser (Hera), Europas plan mot cancer och det europeiska hälsodataområdet.

Som en viktig del av EU:s övergripande svar på dessa utmaningar föreslår kommissionen en omfattande översyn av EU:s läkemedelslagstiftning så att följande fem huvudmål kan uppnås:

1. Säkerställa att alla patienter i EU får snabb och rättvis tillgång till säkra och effektiva läkemedel till rimligt pris.
2. Förbättra försörjningstryggheten och säkerställa att patienter alltid har tillgång till läkemedel, oavsett var i EU de bor.
3. Erbjuda en attraktiv, innovations- och konkurrenskraftsvänlig miljö för forskning, utveckling och produktion av läkemedel i Europa.
4. Göra läkemedel mer miljömässigt hållbara.

[1] Meddelande från kommissionen, *En läkemedelsstrategi för Europa*, COM(2020)761 final.
[2] https://commission.europa.eu/strategy-and-policy/priorities-2019-2024/promoting-our-european-way-life/european-health-union_sv.

5. Motverka antimikrobiell resistens genom en One Health-modell som omfattar människors och djurs hälsa och miljön.

För att dessa mål ska kunna uppnås föreslår kommissionen en reform av EU:s läkemedelslagstiftning, bland annat genom ett förslag till ett nytt direktiv och ett förslag till en ny förordning, för att modernisera och förenkla och ersätta följande befintliga lagstiftning: Direktiv 2001/83/EG[3] och förordning (EG) nr 726/2004[4] (som kallas *den allmänna läkemedelslagstiftningen*), förordning (EG) nr 1901/2006 om läkemedel för pediatrisk användning (*den pediatriska förordningen*)[5] och förordning (EG) nr 141/2000 om särläkemedel[6]. Dessutom föreslår kommissionen en rådsrekommendation om antimikrobiell resistens för att komplettera och stärka EU:s insatser.

En reform av läkemedelslagstiftningen utgör ett tillfälle att skapa en patientcentrerad, framåtblickande och hållbar ram som gynnar patienterna, vårt samhälle och hälso- och sjukvårdssystemen i Europa och samtidigt säkerställer att EU:s industri förblir konkurrenskraftig internationellt. Det kommer att krävas samarbete mellan olika berörda parter för att åstadkomma positiva förändringar. Industrin kommer att spela en grundläggande roll, både för att tillgodose patienternas behov och för att driva på innovation och konkurrenskraft, på ett område där EU måste behålla sitt internationella ledarskap och stärka resiliensen. Den föreslagna reformen bygger på omfattande samråd med alla relevanta berörda parter[7].

I detta meddelande ges en översikt över de viktigaste delarna i den föreslagna reformen av läkemedelslagstiftningen och i den föreslagna rådsrekommendationen om antimikrobiell resistens.

2. En reform som ska ge patienter i hela EU bättre tillgång till läkemedel till rimliga priser

Främja snabb och rättvis tillgång till läkemedel för patienterna

Ett viktigt mål med reformen är att se till att alla patienter i hela EU får snabb och rättvis tillgång till säkra och effektiva läkemedel[8]. Detta är dock inte alltid fallet i dag, särskilt inte när det gäller innovativa läkemedel, eftersom patienternas tillgång varierar beroende på vilket medlemsland de bor i[9].

För att nå ut till patienterna måste läkemedel ha ett godkännande för försäljning och det är det företag som innehar godkännandet som ska lansera det på marknaden. De flesta innovativa läkemedel får ett centralt godkännande för försäljning i EU, vilket gör att de kan saluföras i alla medlemsländer samtidigt. Beslutet om att lansera ett läkemedel i ett visst medlemsland är

[3] Europaparlamentets och rådets direktiv 2001/83/EG av den 6 november 2001 om upprättande av gemenskapsregler för humanläkemedel.
[4] Europaparlamentets och rådets förordning (EG) nr 726/2004 av den 31 mars 2004 om inrättande av unionsförfaranden för godkännande av och tillsyn över humanläkemedel och om inrättande av en europeisk läkemedelsmyndighet.
[5] Europaparlamentets och rådets förordning (EG) nr 1901/2006 av den 12 december 2006 om läkemedel för pediatrisk användning och om ändring av förordning (EEG) nr 1768/92, direktiv 2001/20/EG, direktiv 2001/83/EG och förordning (EG) nr 726/2004.
[6] Europaparlamentets och rådets förordning (EG) nr 141/2000 av den 16 december 1999 om särläkemedel.
[7] Konsekvensbedömningsrapport om översynen av den allmänna läkemedelslagstiftningen, bilaga 2: Samråd med berörda parter.
[8] I enlighet med princip16 i den europeiska pelaren för sociala rättigheter, (EUT C 428, 13.12.2017, s. 10).
[9] Konsekvensbedömningsrapport om översynen av den allmänna läkemedelslagstiftningen, kapitel 2.

dock ett kommersiellt beslut av företaget och det grundas på faktorer som marknadsstorlek, marknadsföring och distributionsnät, samt nationell prissättnings- och ersättningspolitik. I små eller mindre rika medlemsländer kommer därför ett begränsat antal produkter in på marknaden eller också sker det med fördröjning[10].

Syftet med den föreslagna reformen är att göra det lättare för patienter att snabbare få tillgång till innovativa läkemedel i hela EU. Bland åtgärderna ingår också att underlätta för snabba godkännanden för försäljning (se kapitel 4), samtidigt som man säkerställer en grundlig utvärdering av läkemedlens kvalitet, säkerhet och effekt. Dessutom kommer företagen att uppmuntras att lansera sina produkter i alla EU-länder och att utveckla produkter som tillgodoser icke tillgodosedda medicinska behov (se kapitel 4 för närmare uppgifter om rättsliga skyddsincitament och rättsligt stöd).

Den föreslagna reformen kommer också att underlätta snabbare marknadstillträde för generiska läkemedel och biosimilarer. För nya läkemedel som inte kan utnyttja de föreslagna villkorade rättsliga skyddsperioderna (se kapitel 4), kommer marknadstillträdet för konkurrerande generiska läkemedel och biosimilarer att ske snabbare än med de nuvarande reglerna. Dessutom kommer förfarandena för godkännande av generiska läkemedel och biosimilarer att förenklas och därmed påskyndas.

För närvarande finns det redan bestämmelser som gör det möjligt för utvecklare av generiska läkemedel och biosimilarer att genomföra studier för framtida *godkännanden för försäljning* medan originalläkemedlet fortfarande omfattas av patentskydd/tilläggsskydd[11] (så kallade Bolar-undantag). Den föreslagna reformen kommer att bredda dessa bestämmelser och göra dem mer förutsägbara för industrin för generiska läkemedel och biosimilarer genom att genomförandet av bestämmelserna samordnas i hela EU. Rent konkret kommer den att göra det möjligt att genomföra studier till stöd för framtida *prissättning och ersättning* samt tillverkning eller inköp av patentskyddade aktiva substanser i syfte att ansöka om godkännande för försäljning under den perioden, vilket bidrar till att marknadsinträdet för generiska läkemedel och biosimilarer kan ske den dag då patentet/tilläggsskyddet upphör. När det gäller särläkemedel kommer reformen också att säkerställa att generiska läkemedel och biosimilarer kan komma in på marknaden så snart som perioden med ensamrätt på marknaden[12] löper ut.

Ökat samarbete och mer öppenhet för att förbättra läkemedlens prisöverkomlighet

Rimliga priser på läkemedel är en ständig utmaning för EU:s hälso- och sjukvårdssystem och för patienterna som måste betala för dem. För ersättningsgilla läkemedel kan höga priser äventyra hälso- och sjukvårdssystemens finansiella hållbarhet. För läkemedel som inte ersätts fullt ut kan höga priser ha stor inverkan på patienternas ekonomiska situation och leda till direkta negativa hälsokonsekvenser för patienter som inte har råd med dessa läkemedel.

För att göra prissättningen på läkemedel rimligare tillkännagavs i läkemedelsstrategin för Europa åtgärder för att stödja samarbete mellan medlemsländerna vad gäller prissättnings-, ersättnings- och betalningspolitiken, ett område som faller under nationell behörighet. Kommissionen har omvandlat nätverket av behöriga myndigheter för prissättning och ersättning (Network of Competent Authorities on Pricing and Reimbursement, NCAPR) från ett tillfälligt forum till en plattform för kontinuerligt frivilligt samarbete. Kommissionen är

[10] Konsekvensbedömningsrapport om översynen av den allmänna läkemedelslagstiftningen, kapitel 2 och bilaga 14.

[11] Se kapitel 4 för mer information om immateriella rättigheter som patent och tilläggsskydd.

[12] Se kapitel 4 för mer information om rättsligt skydd som ensamrätt på marknaden.

fast besluten att intensifiera detta samarbete och ytterligare stödja informationsutbytet mellan nationella myndigheter, bland annat om offentlig upphandling av läkemedel, samtidigt som medlemsländernas befogenheter på detta område respekteras fullt ut.

Gemensam upphandling av läkemedel kan vara en framgångsrik form av ökat samarbete för att förbättra prisöverkomligheten, tillgången till läkemedel och försörjningstryggheten. Detta har visat sig genom den gemensamma upphandlingen av covid-19-behandlingar och vacciner mot apkoppor[13]. Medlemsländer som är intresserade av gemensam upphandling av läkemedel kan använda tillgängliga regleringsverktyg enligt gällande EU-regler, såsom direktivet om offentlig upphandling[14], avtalet om gemensam upphandling[15] och budgetförordningen[16] som för närvarande håller på att ses över. På begäran av medlemsländerna är kommissionen beredd att ytterligare stödja och underlätta tillgången till läkemedel för europeiska patienter, särskilt när det gäller läkemedel mot sällsynta och kroniska sjukdomar.

Den föreslagna reformen av läkemedelslagstiftningen omfattar ett antal åtgärder som kommer att bidra till rimligare pris. Åtgärder för att underlätta snabbare marknadstillträde för generiska läkemedel och biosimilarer kommer att öka konkurrensen mellan läkemedel, sänka priserna på dem, främja rimliga priser för patienterna och gynna hälso- och sjukvårdssystemens hållbarhet. Dessutom kommer genereringen av jämförande kliniska data att uppmuntras för att ytterligare stärka bedömningen av läkemedel och stödja beslut om prissättning och ersättning i senare led. Ett förbättrat samarbete mellan myndigheter med ansvar för godkännande för försäljning, utvärdering av medicinsk teknik[17,18] och prissättning och ersättning kommer att främja en mer enhetlig strategi i frågor som evidensgenerering under läkemedlets hela livscykel (se kapitel 4).

Insyn i den offentliga finansieringen skulle också kunna bidra till att sänka läkemedelspriserna. I dag är storleken på det offentliga ekonomiska stöd som har bidragit till forskning och utveckling av ett visst läkemedel oklar. Denna brist på insyn i de risker som bärs av allmänheten, i motsats till investeraren, skapar ojämlika villkor mellan industrin och prissättnings- och ersättningsmyndigheterna under förhandlingarna. Som svar på starka krav från patientorganisationer och andra berörda parter kommer den föreslagna reformen att innebära åtgärder för ökad insyn kring offentlig finansiering av läkemedelsutveckling. Enligt den föreslagna reformen kommer läkemedelsföretag att bli skyldiga att offentliggöra information om allt direkt ekonomiskt stöd som de tar emot från en myndighet eller ett offentligt finansierat organ till stöd för forskning och utveckling av läkemedel. Den här informationen ska vara lätt åtkomlig för allmänheten på en särskild webbsida för företaget och genom databasen över humanläkemedel som är godkända i unionen. Sådan insyn förväntas i sin tur att stödja medlemsländerna i deras förhandlingar med läkemedelsföretagen, och i slutändan göra läkemedel mer prisöverkomliga.

[13] Kommissionen har offentliggjort en studie om offentliga upphandling av läkemedel med rekommendationer för att optimera (gemensam) upphandling. Finns på: https://data.europa.eu/doi/10.2925/044781.
[14] Europaparlamentets och rådets direktiv 2014/24/EU av den 26 februari 2014 om offentlig upphandling och om upphävande av direktiv 2004/18/EG.
[15] Europaparlamentets och rådets förordning (EU) 2022/2371 av den 23 november 2022 om allvarliga gränsöverskridande hot mot människors hälsa och om upphävande av beslut nr 1082/2013/EU.
[16] Förslag till Europaparlamentets och rådets förordning om finansiella regler för unionens allmänna budget (omarbetning), COM(2022) 223 final.
[17] Vid utvärdering av medicinsk teknik utvärderas mervärdet av nya läkemedel jämfört med befintliga.
[18] Europaparlamentets och rådets förordning (EU) 2021/2282 av den 15 december 2021 om utvärdering av medicinsk teknik och om ändring av direktiv 2011/24/EU.

Stöd till rimligare priser på läkemedel

- Underlätta snabbare marknadsinträde för generiska läkemedel och biosimilarer för att öka konkurrensen och därmed sänka priserna.
- Stimulera genereringen av jämförande kliniska data för att stödja medlemsländerna att fatta snabbare och evidensbaserade beslut om prissättning och ersättning.
- Öka insynen kring offentlig finansiering av läkemedelsutveckling för att stödja medlemsländerna i deras prisförhandlingar med läkemedelsföretagen.
- Genom andra åtgärder än lagstiftning stödja samarbete om prissättning och ersättning mellan de nationella behöriga myndigheterna, genom utbyte av information och bästa praxis om nationell prissättnings- och upphandlingspolitik.

3. Förbättrad läkemedelsförsörjning och hantering av brister

Läkemedelsbrist har blivit ett växande folkhälsoproblem i många EU-länder[19], men också globalt. Brister utgör potentiella allvarliga risker för patienternas hälsa och påverkar deras rätt till lämplig medicinsk behandling. Det har under de senaste åren signalerats om ökande läkemedelsbrist, både i parlamentets resolutioner[20] och i rådets slutsatser[21] och från medlemsländerna och berörda parter.

Den strukturerade dialogen om försörjningstrygghet för läkemedel[22] och den senaste tidens händelser, såsom covid-19-pandemin, Rysslands militära angrepp på Ukraina och den höga inflationstakten, har lyft fram frågor om försörjningstryggheten för läkemedel i EU. Såsom konstateras i kommissionens studie om läkemedelsbrist har bristerna flera olika orsaker och vissa utmaningar har identifierats längs hela värdekedjan för läkemedel, även när det gäller tillverkning[23]. Brist på läkemedel kan framför allt uppstå på grund av leveranskedjornas ökade komplexitet och specialisering, bristande geografisk diversifiering när det gäller anskaffningen av vissa viktiga ingredienser och läkemedel, och lagstiftningen som upplevs som komplicerad. EU:s beroende[24] av ett begränsat antal tredjeländer för att producera ingredienser och läkemedel ökar och utgör potentiella sårbarheter i leveranskedjan.

De viktigaste inslagen i det tillhörande arbetsdokumentet från kommissionens avdelningar[25] om sårbarheten i de globala leveranskedjorna för läkemedel tas upp i den föreslagna reformen, men ett antal andra åtgärder har också inletts eller planeras för att hantera de utmaningar som identifierades genom den processen. Som angavs i arbetsdokumentet från kommissionens avdelningar ger industristrategierna[26,27] redan en stark grund för att förbättra

[19] Se till exempel betänkande från Europaparlamentets utskott för miljö, folkhälsa och livsmedelssäkerhet av den 22 juli 2020, Brist på läkemedel – hantering av ett växande problem, 2020/2071 (INI).
[20] Exempelvis Europaparlamentets resolution av den 17 september 2020 om läkemedelsbristen – att hantera ett växande problem, 2020/2071(INI), skäl G.
[21] Exempelvis rådets slutsatser om tillgång till läkemedel och medicintekniska produkter för ett starkare och mer resilient EU, 2021/C 269 I/02, skäl 5.
[22] https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe/structured-dialogue-security-medicines-supply_sv.
[23] https://op.europa.eu/sv/publication-detail/-/publication/1f8185d5-5325-11ec-91ac-01aa75ed71a1/language-en/format-PDF/source-245338952.
[24] Det är framför allt Kina och Indien som håller på att bli stora tillverkare av insatsvaror för läkemedelsindustrin, och de utgör produktionscentrumet i Asien. Produktionen är inte bara koncentrerad regionalt, utan för många ingredienser är den också begränsad till ett fåtal tillverkare i dessa länder.
[25] https://health.ec.europa.eu/system/files/2022-10/mp_vulnerabilities_global-supply_swd_en.pdf.
[26] Meddelande från kommissionen, *En ny industristrategi för EU*, COM(2020) 102 final.

försörjningstryggheten för läkemedel. Framtida arbete kommer också att fokuseras på att främja grön innovation, digital innovation och ökat samarbete mellan nyckelaktörer både inom EU och globalt. Kommissionen stöder också medlemsstaternas insatser för att slå samman sina offentliga resurser via viktiga projekt av gemensamt europeiskt intresse på hälsoområdet för att främja utvecklingen av innovativ, ekonomiskt och miljömässigt hållbar teknik som går utöver den senaste tekniken inom sektorn och gör det möjligt att åtgärda marknadsmisslyckanden.

Som en del av byggstenarna i den europeiska hälsounionen och för att åtgärda vissa av de svagheter som avslöjades under covid-19-pandemin utvidgades mandatet för Europeiska läkemedelsmyndigheten (EMA)[28] för att möjliggöra samordning och hantering av specifika läkemedelsbrister under kriser. Dessutom inrättades Myndigheten för beredskap och insatser vid hälsokriser (Hera)[29] för att säkerställa tillgång till de medicinska motåtgärder som behövs vid hot mot folkhälsan på unionsnivå och för att hantera marknadsutmaningar med hjälp av åtgärder som övervakning av försörjningskedjan, lageruppbyggnad[30] och offentlig upphandling. Som en del av leveranskedjorna kommer den föreslagna akten om kritiska råvaror[31] att säkerställa tillgången till vissa material som är relevanta för tillverkningen av läkemedel.

Även om effektiva processer har inrättats på detta område finns det ett tydligt behov av ökad samordning i hela EU och av lämpliga åtgärder för att trygga tillgången på läkemedel för EU-medborgarna, inte bara i krissituationer utan även under normala förhållanden.

I reformen föreslås åtgärder för att hantera utmaningar i fråga om tillgång utöver dem som ingår i EMA:s utvidgade mandat och i Heras uppgifter, som är begränsade till krisberedskap och krishantering. Den kommer att åtgärda systembrister och öka försörjningstryggheten för kritiska läkemedel genom strängare krav på leveranser, tidigare anmälan av brister och tillbakadraganden och en starkare roll för EMA när det gäller samordning av åtgärder mot brister. Inom ramen för den föreslagna reformen kommer dessutom de läkemedel som anses vara mest kritiska för EU:s hälso- och sjukvårdssystem att tas upp i en EU-förteckning. På så sätt kommer man att kunna analysera sårbarheter i leveranskedjan för dessa läkemedel, följt av rekommendationer om åtgärder som innehavare av godkännande för försäljning, medlemsländer eller andra enheter ska vidta för att förbättra försörjningstryggheten (t.ex. beredskapslager som ska upprätthållas). I detta sammanhang måste medlemsstaterna också rapportera till EMA vilka åtgärder de har vidtagit för att stärka tillgången på det läkemedlet.

Då kan EU effektivt förebygga försörjningsproblem och säkerställa kontinuitet i försörjningen av dessa läkemedel till EU-medborgarna.

Kontinuerlig hantering av läkemedelsbrist och problem i leveranskedjorna

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[27] Meddelande från kommissionen, *Uppdatering av industristrategin 2020: en starkare inre marknad för EU:s återhämtning*, COM(2021) 350 final.

[28] https://eur-lex.europa.eu/legal-content/sv/TXT/?toc=OJ:L:2022:020:TOC&uri=uriserv:OJ.L_.2022.020.01.0001.01.sv.

[29] https://health.ec.europa.eu/system/files/2021-09/hera_2021_decision_en_0.pdf.

[30] Hera har en budget på 1,2 miljarder euro för lagring av medicinska motåtgärder inom ramen för rescEU. En del av denna budget kommer att användas för att lagra antibiotika, samtidigt som man ser till att inte förvärra de befintliga bristerna. Den lagrade antibiotikan kan vid behov spridas till medlemsländerna genom EU:s civilskyddsmekanism.

[31] Proposal for a Regulation of the European Parliament and of the Council establishing a framework for ensuring a secure and sustainable supply of critical raw materials and amending Regulations (EU), COM(2023)160 final.

- Genom den föreslagna reformen införs krav på att behöriga myndigheter på nationell nivå och EMA kontinuerligt ska övervaka läkemedelsbrister. Skyldigheterna för innehavare av godkännande för försäljning kommer att skärpas, bland annat genom tidigarelagd och samordnad rapportering av läkemedelsbrister och upprätthållande av planer för att förebygga brister.
- EMA kommer att få en starkare samordnande roll för att övervaka och hantera kritiska läkemedelsbrister på EU-nivå, tillsammans med den verkställande styrgruppen för läkemedelsbrist och läkemedelssäkerhet. I detta sammanhang måste medlemsstaterna också rapportera till EMA om alla planerade eller vidtagna åtgärder på nationell nivå för att minska eller avhjälpa bristen på ett visst läkemedel. Insyn i brister ska uppnås genom offentliggörande av information om läkemedelsbrist på nationell nivå och EU-nivå.
- Kommissionen kommer att upprätta en EU-omfattande förteckning över kritiska läkemedel, och sårbarheten i leveranskedjan för dessa läkemedel ska bedömas.
- När det gäller kritiska brister måste innehavare av godkännande för försäljning av läkemedel arbeta för att åtgärda dessa brister enligt rekommendationer, och rapportera resultaten av de åtgärder som vidtagits. Sådana rekommendationer kan till exempel vara att öka eller omorganisera tillverkningskapaciteten eller anpassa distributionen för att förbättra tillgången.

4. En reform som främjar innovation och EU:s konkurrenskraft

Ändamålsenliga incitament för innovation, tillgång och hantering av icke tillgodosedda medicinska behov

Efter USA är EU världens största läkemedelsmarknad, och läkemedelsindustrin i EU är stark och konkurrenskraftig. Det är en av Europas högst presterande högteknologiska sektorer och sysselsätter direkt 840 000 personer och tre gånger fler indirekt i tidigare och senare led. Europa (EU, Storbritannien och Schweiz) är den nästa största investeraren i forskning och utveckling på läkemedelsområdet, med 39,7 miljarder euro 2020, efter USA med investeringar på 63,5 miljarder euro[32]. När det gäller tillverkning av högteknologiska läkemedel är EU en tydlig global ledare, vilket också framgår av EU:s ledande roll med att förse världen med covid-19-vacciner. Under 2021 exporterade EU läkemedel till ett värde av 235 miljarder euro, vilket är 136 miljarder euro mer än dess import[33]. EU satsar omkring 1,5 % av sin BNP på läkemedel, eller 230 miljarder euro under 2021, varav över 80 % går till innovativa produkter[34]. EU:s läkemedelsmarknad står för 17 % av den globala marknaden, vilket gör den till den näst mest attraktiva marknaden för branschen, särskilt för innovatörer.

Reformen av läkemedelslagstiftningen syftar till att upprätthålla och stärka ställningen för EU:s läkemedelsindustri, både inom EU och globalt. Regelverket kommer att fortsätta att stödja innovation och säkerställa att patienterna i EU kan dra nytta av den modernaste hälso- och sjukvården och de senaste läkemedlen. Under covid-19-pandemin visade det sig att innovation är avgörande när det gäller att utveckla nya och bättre behandlingar, inbegripet nya läkemedel och nya användningsområden för befintliga läkemedel.

Det är en komplicerad process att bedriva läkemedelsforskning och det innebär betydande kostnader och risker för utvecklarna (t.ex. kostnaden för och den vetenskapliga komplexiteten

[32] The Pharmaceutical Industry in Figures, Key Data, EFPIA, 2022.
[33] Trade surplus in medicinal products records high, Eurostat, 2022.
[34] IQVIA MIDAS – databas.

inom preklinisk och klinisk forskning). Dessutom råder det internationell konkurrens för att locka till sig forskning och utveckling genom att erbjuda inte bara en framtidssäkrad och stabil rättslig ram utan också en gynnsam miljö. Frågor som tillgång till kapital, tillgänglig infrastruktur och kompetent och kvalificerad arbetskraft är viktiga faktorer för utveckling av läkemedel och för att driva på innovation. Vid översynen av läkemedelslagstiftningen tas hänsyn till EU:s konkurrenskraft, både vad gäller regelverk och industripolitik. Det ska finnas en lämplig balans mellan främjandet av innovation, tillgång till läkemedel och deras prisöverkomlighet. Utvecklingen av nya läkemedel och tillgången till de läkemedel som våra hälso- och sjukvårdssystem behöver är beroende av en framgångsrik läkemedelsindustri som är en viktig tillgång för EU:s ekonomi.

I EU kompletteras ett starkt system för immateriella rättigheter (patent och tilläggsskydd[35]) med rättsliga skyddsincitament i läkemedelslagstiftningen. Såväl immateriella rättigheter och rättsliga skyddsincitament skyddar och främjar innovation och kompenserar för de risker och kostnader som utvecklare av innovativa läkemedel ådrar sig. Samtidigt ger det här systemet en tydlig ram så att generiska läkemedel och biosimilarer kan komma in på marknaden så snart de relevanta immateriella rättigheterna och de lagstadgade skyddsperioderna upphör.

Läkemedel kan skyddas av patent och tilläggsskydd enligt nationella, europeiska och internationella rättsliga ramar, inbegripet EU:s förordning om tilläggsskydd[36]. Detta skydd kan räcka i över 20 år från det att det första patentet lämnas in, vanligen i ett tidigt skede av läkemedelsutvecklingen. Från och med godkännandet för försäljning ger EU:s läkemedelslagstiftning dessutom 10 års rättsligt skydd till innovativa läkemedel, vilket omfattar 8 år av lagstadgat uppgiftsskydd[37] och 2 års marknadsskydd[38]. Denna period kan förlängas upp till 11 år om en ny behandlingsindikation läggs till efter det ursprungliga godkännandet för försäljning. När det gäller läkemedel för sällsynta sjukdomar (särläkemedel), tilldelas innovativa läkemedel 10 års ensamrätt på marknaden[39]. Förutom ovanstående skydd får läkemedel som har följt den pediatriska utvecklingsplan som avtalats med EMA sex månaders förlängning av sitt tilläggsskydd.

Tillsammans utgör immateriella rättigheter och rättsligt skydd i EU ett starkt system för innovation. Det är ett mycket konkurrenskraftigt skydd jämfört med skyddet i andra länder runt om i världen.

I de nuvarande investeringarna i läkemedelsutveckling prioriteras dock inte alltid de största icke tillgodosedda medicinska behoven. Detta gäller särskilt sjukdomar som ställs inför vetenskapliga utmaningar (t.ex. begränsad förståelse för sjukdomen, begränsad grundforskning) eller begränsat kommersiellt intresse (t.ex. sällsynta sjukdomar). Därför finns det allvarliga sjukdomar, som vissa cancerformer eller neurodegenerativa sjukdomar, för vilka tillfredsställande behandlingar fortfarande saknas. Dessutom finns det över 6 000

[35] Tilläggsskyddet är en immateriell rättighet som fungerar som en förlängning av en patenträttighet.

[36] Europaparlamentets och rådets förordning (EG) nr 469/2009 av den 6 maj 2009 om tilläggsskydd för läkemedel.

[37] Lagstadgat dataskydd avser perioden efter det att det ursprungliga godkännandet av ett läkemedel, då företag som vill utveckla generiska eller biosimilara versioner av läkemedlet inte kan hänvisa till resultaten av de prekliniska försök och de kliniska prövningar av läkemedlet som ingår i den ursprungliga dokumentationen.

[38] Marknadsskydd avser en period under vilken ansökningar om godkännande för försäljning av generiska läkemedel och biosimilarer kan lämnas in och bedömas och respektive godkännande för försäljning kan beviljas. Den generiska eller biosimilara produkten kan dock endast släppas ut på marknaden efter det att den perioden har löpt ut.

[39] Ensamrätt på marknaden avser perioden efter godkännande för försäljning då liknande läkemedel för samma indikation inte kan släppas ut på marknaden.

kända ovanliga sjukdomar[40] varav 95 % för närvarande saknar behandlingsalternativ[41]. När det gäller läkemedel för barn har stora framsteg gjorts på områden där behoven hos barn och vuxna överlappar varandra, eftersom utvecklingen fortfarande styrs av vuxnas behov. I de fall där sjukdomarna är biologiskt olika hos vuxna och barn, som barncancer, psykiska och beteendemässiga störningar eller neonatala tillstånd, har endast ett begränsat antal läkemedel utvecklats.

Även när innovativa läkemedel har utvecklats och godkänts är det inte alla patienter i EU som får tillgång till dem i tid.

Den föreslagna reformen av läkemedelslagstiftningen kommer att flytta det rättsliga skyddssystemet från en universallösning till en mer målinriktad strategi som främjar patienternas tillgång till läkemedel till rimliga priser i alla EU-länder, och hanterar icke tillgodosedda medicinska behov. Innovation på områden med icke tillgodosedda medicinska behov kommer också att främjas av ett riktat regleringsstöd från EMA (läs mer om ett förstärkt system för prioriterade läkemedel som diskuteras i nästa avsnitt).

Enligt den föreslagna reformen kommer innovativa läkemedel fortfarande att omfattas av en standardperiod för rättsligt skydd som kommer att vara något kortare än i dag, men som kan förlängas om produkten uppfyller vissa folkhälsomål (se nedanstående ruta). Med de ytterligare villkorade skyddsperioderna kommer den längsta tid för rättsligt skydd som kan beviljas att bli ännu längre än i dag. Enligt den föreslagna reformen kan de lagstadgade skyddsperioderna uppgå till högst 12 år för innovativa läkemedel (om en ny behandlingsindikation läggs till efter det ursprungliga godkännandet för försäljning), medan de i dag är högst 11 år. För särläkemedel som tillgodoser ett stort icke tillgodosett medicinskt behov kan de lagstadgade skyddsperioderna uppgå till högst 13 år, medan de i dag är högst 10 år.

EU kommer därmed att fortsätta att erbjuda ett av de mest attraktiva regelverken i världen. Andra länder erbjuder i genomsnitt 6 år (Israel och Kina) till 8 år (Japan och Kanada) för rättsligt skydd.

Mer målinriktade incitament för innovation med fokus på patienternas tillgång och icke tillgodosedda medicinska behov

- Enligt den föreslagna reformen kommer den kortaste lagstadgade skyddsperioden för innovativa läkemedel att vara 8 år, vilket omfattar 6 år av dataskydd och 2 år av marknadsskydd. Företag kan få ytterligare dataskyddsperioder om de lanserar läkemedlet i alla medlemsländer (ytterligare 2 år) eller om de utvecklar ett läkemedel som tillgodoser icke tillgodosedda medicinska behov (ytterligare 6 månader) eller genomför kontrollerade kliniska prövningar (ytterligare sex månader). Ytterligare ett års dataskydd kan beviljas för en ny behandlingsindikation.
- Dessa nya regler om rättsligt skydd kommer också att gälla för pediatriska läkemedel. Dessutom kommer läkemedel som har följt det pediatriska utvecklingsprogram som överenskommits med EMA även fortsättningsvis att få en förlängning med sex månader av sitt tilläggsskydd. Reglerna om pediatriska utvecklingsprogram kommer också att

[40] https://www.orpha.net/consor/cgi-bin/Education_AboutRareDiseases.php?lng=SV.

[41] Joint evaluation of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products (inte översatt till svenska) (SWD(2020) 163 final).

anpassas för att ytterligare stimulera forskning och utveckling av läkemedel mot sjukdomar som endast drabbar barn.

- Särskilda bestämmelser kommer att gälla för särläkemedel för att främja forskning och utveckling på området sällsynta sjukdomar. Standardperioden för ensamrätt på marknaden för särläkemedel kommer att vara 9 år. Företag kan få ytterligare perioder med ensamrätt på marknaden om de uppfyller ett stort icke tillgodosett medicinskt behov (ytterligare 1 år), lanserar läkemedlet i alla medlemsländer (ytterligare 1 år) eller utvecklar nya behandlingsindikationer för ett redan godkänt särläkemedel (upp till 2 extra år).
- Det ytterligare rättsliga skyddet för lanseringen på marknaden i alla medlemsländer kommer att beviljas om läkemedlet levereras i tillräckliga mängder i alla medlemsländer inom två år efter det att godkännandet för försäljning har beviljats, eller inom tre år för företag med begränsad erfarenhet av EU-systemet, t.ex. små och medelstora företag. Om ett medlemsland utfärdar ett undantag (t.ex. för att landet vill att lanseringen på marknaden ska äga rum vid en senare tidpunkt), kommer det ytterligare rättsliga skyddet fortfarande att beviljas.
- Nya användningsområden för befintliga läkemedel kan omfattas av fyra års uppgiftsskydd. Dessutom kommer icke-vinstdrivande enheter att kunna lämna in belägg till EMA till stöd för nya indikationer som tillgodoser icke tillgodosedda medicinska behov för redan godkända läkemedel.

Det är viktigt att notera att den föreslagna reformen av läkemedelslagstiftningen inte kommer att påverka skyddet av immateriella rättigheter (patent och tilläggsskydd). I detta avseende lägger kommissionen samtidigt fram en reform av förordningen om tilläggsskydd, som kommer att skapa ett centraliserat prövningsförfarande för beviljande av nationella tilläggsskydd och ett enhetligt tilläggsskydd för läkemedel, utan att innehållet i de tillämpliga reglerna ändras (t.ex. villkor för berättigande, giltighetstid osv.). För dem som ansöker om tilläggsskydd kommer den föreslagna reformen att minska kostnaderna och den administrativa bördan avsevärt i det nuvarande systemet med tilläggsskydd, som för närvarande genomförs på en rent nationell nivå. Genom att rättssäkerheten och insynen i systemet för tilläggsskydd ökar kommer detta initiativ också att gynna tillverkare av generiska produkter. Initiativet kommer också att säkerställa att branschen för innovativa läkemedel kan dra nytta av fördelarna med det enhetliga patentet genom ett motsvarande enhetligt tilläggsskydd.

Sammanfattningsvis kommer kombinationen av patent och tilläggsskydd och rättsligt skydd även fortsättningsvis att skydda EU:s konkurrensfördel globalt i fråga om läkemedelsutveckling, samtidigt som forskning och utveckling styrs mot de största patientbehoven och säkerställer snabbare och rättvisare tillgång till läkemedel i hela EU.

Belöning av innovation på områden med icke tillgodosedda medicinska behov genom ökat regleringsstöd för utveckling av lovande läkemedel

EMA erbjuder vetenskapligt stöd till läkemedelsutvecklare om det lämpligaste sättet att generera tillförlitliga belägg för ett läkemedels fördelar och risker (t.ex. vetenskaplig vägledning om utformningen av kliniska prövningar) i syfte att stödja en snabb och sund utveckling av högkvalitativa, effektiva och säkra läkemedel som gynnar patienterna.

Den föreslagna reformen kommer ytterligare att stärka det vetenskapliga stödet från EMA, särskilt för lovande läkemedel som är under utveckling för icke tillgodosedda medicinska behov, utifrån de erfarenheter som erhållits från systemet för prioriterade läkemedel

(Prime)[42]. Sådana prioriterade läkemedel kommer att få ökat vetenskapligt stöd och regleringsstöd och kommer att omfattas av påskyndade bedömningsmekanismer. Detta förstärkta Prime-system kommer att främja innovation inom områden med icke tillgodosedda medicinska behov, göra det möjligt för läkemedelsföretag att påskynda utvecklingsprocessen och ge patienterna snabbare tillgång till läkemedel.

Genom reformen kommer det dessutom att bli lättare att använda läkemedel utan patentskydd till nya behandlingsområden, med ett särskilt stödsystem från EMA för små och medelstora företag och icke-vinstdrivande utvecklare.

Reformen kommer också att påskynda bedömningen av lovande läkemedel genom att ge möjlighet till löpande granskning, där data granskas allteftersom de blir tillgängliga. Denna strategi visade sig ändamålsenlig under covid-19-pandemin och reformen syftar till att utvidga den till lovande läkemedel som erbjuder exceptionella behandlingsmässiga framsteg på områden med icke tillgodosedda medicinska behov. Ett tillfälligt nödgodkännande för försäljning på EU-nivå kommer att införas för hot mot folkhälsan på unionsnivå där det finns ett stort intresse för att utveckla och godkänna säkra och effektiva läkemedel så snabbt som möjligt.

Förbättrat regelverk så att Europa förblir attraktivt för investerare och innovatörer

Ett effektivt och smidigt EU-regelverk spelar en avgörande roll för att stödja utvecklingen och ett snabbt godkännande av läkemedel och för patienternas tillgång till dem. Det skapar också en gynnsam miljö för att öka läkemedelsindustrins innovationskapacitet och konkurrenskraft.

För närvarande omfattar den vetenskapliga utvärderingen av läkemedel för EU-godkännande för försäljning betydande ”klockstopp”, under den tid då företag utarbetar svar på EMA:s förfrågningar om information som saknas i den ursprungliga ansökan. Den föreslagna förstärkningen av EMA:s vetenskapliga stöd till läkemedelsutvecklare, innan ansökningar om godkännande för försäljning lämnas in, kommer att förbättra kvaliteten på de ursprungliga ansökningarna, minska förseningar som orsakas av klockstopp och påskynda utvärderingen för godkännande för försäljning. Ofullständiga ansökningar kommer att ogiltigförklaras under utvärderingen om de sökande inte inom fastställda tidsfrister lämnar in de uppgifter som saknas. Detta kommer att frigöra resurser och optimera utvärderingssystemet. Med reformen föreslås dessutom att den vetenskapliga bedömningstiden ska minska från dagens 210 dagar till 180 dagar, och kommissionens tid för att godkänna läkemedlet ska minska från 67 till 46 dagar. För läkemedel som är av stort intresse ur folkhälsosynpunkt kommer bedömningstiden att bli 150 dagar. Dessa kortade tidsramar tillsammans med ovan nämnda stödåtgärder kommer att säkerställa att läkemedlen snabbare når patienterna.

Dessutom kommer den föreslagna reformen att förbättra EMA:s struktur och styrning genom att strukturen hos dess vetenskapliga kommittéer förenklas och den expertisbaserade kapaciteten ökar. Det kommer att undvika dubbelarbete, öka effektiviteten och korta bedömningstiderna för läkemedlen, samtidigt som man upprätthåller hög standard och vetenskaplig sakkunskap. Reformen omfattar också olika åtgärder för att förenkla regleringsförfarandena och främja digitalisering. Detta kommer att minska arbetsbördan för både läkemedelsutvecklare och behöriga myndigheter (se rutan nedan).

[42] https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines.

Små och medelstora företag och icke-vinstdrivande enheter som är involverade i läkemedelsutveckling kommer särskilt att gynnas av den föreslagna reformen eftersom det kommer att minska deras regelbörda. EMA kommer också att erbjuda riktat vetenskapligt stöd och regleringsstöd, däribland minskade avgifter eller undantag, till små och medelstora företag och icke-vinstdrivande enheter.

Regleringsstöd och förenklingar som minskar regelbördan

- Stärka EMA:s tidiga regleringsstöd, särskilt för lovande läkemedel under utveckling för icke tillgodosedda medicinska behov.
- Införa möjligheten för EMA att granska data i faser, allteftersom de blir tillgängliga, för lovande läkemedel som erbjuder en exceptionell terapeutisk utveckling på områden med icke tillgodosedda medicinska behov.
- Införa ett tillfälligt nödgodkännande för försäljning på EU-nivå vid hot mot folkhälsan på unionsnivå om det finns ett stort intresse för att utveckla och godkänna säkra och effektiva läkemedel så snabbt som möjligt.
- Optimera EMA:s struktur (t.ex. färre vetenskapliga kommittéer), med fokus på sakkunskap och kapacitetsuppbyggnad inom nätverket av behöriga myndigheter.
- Förenkla regleringsförfarandena (t.ex. avskaffa förnyelsen av godkännanden för försäljning i de flesta fall) och kraven för godkännande av generiska läkemedel och biosimilarer.
- Korta EMA:s bedömningstid från dagens 210 dagar (i praktiken i genomsnitt 400 dagar) till 180 dagar, och kommissionens tid för att godkänna läkemedlet från 67 till 46 dagar. Dessutom kan produkter som tillgodoser icke tillgodosedda medicinska behov och som är av stor betydelse för folkhälsan omfattas av ett påskyndat förfarande och bedömas inom 150 dagar.
- Digitalisering (t.ex. elektronisk inlämning av ansökningar, elektronisk produktinformation).

Den förbättrade EMA-strukturen i kombination med det förstärkta vetenskapliga stödet från EMA, förenklade förfaranden och digitalisering kommer att minska tiden som behövs för att utvärdera och godkänna läkemedel. Det kommer att bidra till att förbättra konkurrenskraften i EU:s regelverk, och samtidigt underlätta snabb tillgång till innovativa läkemedel, generiska läkemedel och biosimilarer för patienterna.

Dessutom kommer ett antal framtidssäkringsåtgärder att säkerställa att regelverket kan hålla jämna steg med de vetenskapliga och tekniska framstegen och skapa ett gynnsamt regelverk för lovande nya behandlingar och banbrytande innovation, i linje med innovationsprincipen[43]. Detta omfattar också att främja innovativa metoder, inbegripet sådana som syftar till att minska antalet djurförsök. Reformen innebär att möjligheten till regulatoriska sandlådor på läkemedelsområdet kommer att tillåtas för första gången. Dessa ger en strukturerad testmiljö där innovativa metoder och nya läkemedel kan testas under tillsyn av myndigheter. Regulatoriska sandlådor ger tillfälle att skaffa kunskap inte bara om innovation utan också om de regler och bestämmelser som ligger till grund för den och hur dessa bäst kan tillämpas på framtida teknik. Lärdomarna från dessa sandlådor kan med tiden omsättas i anpassade regelverk, vilket är en annan ny del av reformen, och på så sätt skapa anpassade övergripande

[43] https://research-and-innovation.ec.europa.eu/law-and-regulations/ensuring-eu-legislation-supports-innovation_sv.

regler som tillgodoser de lagstadgade standarder som krävs, samtidigt som hänsyn tas till innovativa delar.

Sekundär användning av hälsodata har potential att öka effektiviteten och ändamålsenligheten för läkemedelsutvecklingen, minska kostnader och förbättra patientresultaten. Hälsodata kan till exempel användas för att identifiera icke tillgodosedda medicinska behov, optimera utformningen av kliniska prövningar och stödja framtagningen av underlag för godkännande för försäljning. Dessutom kan real world-data användas för att övervaka läkemedels säkerhet och effektivitet under en period efter det att godkännande för försäljning beviljats och för att stödja kontinuerligt lärande och förbättring inom hälso- och sjukvård. Reformen av läkemedelslagstiftningen tillsammans det europeiska hälsodataområdet kommer att underlätta tillgången till och användningen av hälsodata, samtidigt som patienternas integritet skyddas. Om det blir möjligt med sekundär användning av hälsodata för regleringsändamål kommer det att erbjuda en unik möjlighet till innovation och ökad konkurrenskraft för läkemedelsindustrin i EU.

Framtidssäkrat regelverk

- Underlätta användningen av real-world evidence och av hälsodata för regleringsändamål samtidigt som patienternas integritet skyddas.
- Ökad tydlighet om samspelet mellan EU:s lagstiftningsram för läkemedel och annan medicinsk teknik (t.ex. medicintekniska produkter, ämnen av mänskligt ursprung).
- Regulatoriska sandlådor för testning av nya regleringsmetoder för ny teknik före den formella regleringen.
- Anpassade ramar med specifika rättsliga krav som är avpassade efter vissa nya läkemedels egenskaper.
- Främja användningen av nya metoder för att minska antalet djurförsök.

Den föreslagna reformen kommer att främja samarbete mellan olika myndigheter i EU som är involverade i olika aspekter av ett läkemedels livscykel. EMA kommer exempelvis att samordna en mekanism som ska underlätta utbyte av information och kunskap om vetenskapliga och tekniska frågor av gemensamt intresse mellan myndigheter med ansvar för godkännande för försäljning, kliniska prövningar, utvärdering av medicinsk teknik (HTA) och prissättning och ersättning för läkemedel i EU. Detta kommer att möjliggöra en enhetligare strategi i frågor som icke tillgodosedda medicinska behov och evidensgenerering under läkemedlets hela livscykel. Reformen kommer också att underlätta samarbete mellan EMA och andra EU-byråer, t.ex. på kemikalieområdet, i enlighet med strategin ”ett ämne, en bedömning”.

Farmaceutiska kommittén[44] kommer att fungera som diskussionsforum för politiska frågor som rör läkemedel, som tillämpningen av reglerna om incitament för marknadsintroduktion, för att säkerställa ökad dialog, nära samverkan och ett proaktivt informationsutbyte mellan medlemsländerna och kommissionen. Andra nationella myndigheter (t.ex. för utvärdering av medicinsk teknik, prissättning och ersättning) kan bjudas in att delta i diskussioner i Farmaceutiska kommittén. Åtgärderna för samarbete mellan offentliga myndigheter kommer att förbättra den politiska samstämmigheten och skapa en mer förutsägbar och enhetlig miljö för investerare och innovatörer i EU.

[44] Rådets beslut 75/320/EEG av den 20 maj 1975 om inrättandet av en farmaceutisk kommitté.

På det hela taget utgör dessa reformer ett viktigt steg mot ett effektivare och mer ändamålsenligt regelverk som är bättre rustat för att hantera nya utmaningar och stödja läkemedelssektorns konkurrenskraft och innovation som gynnar patienterna i EU.

5. Miljömässigt hållbarare läkemedel

För att uppnå ambitionerna om miljömässig hållbarhet i läkemedelsstrategin och i andra initiativ i den europeiska gröna given[45] (t.ex. EU:s handlingsplan: *Med sikte på nollförorening av luft, vatten och mark*[46]), måste läkemedelsindustrin begränsa produkternas och processernas negativa effekter på miljön, den biologiska mångfalden och människors hälsa.

Vetenskapliga belägg visar att läkemedel förekommer i miljön på grund av tillverkning, patientanvändning och olämpligt bortskaffande av oanvända eller utgångna produkter[47]. Det faktum att antimikrobiella medel har upptäckts i avloppsrening, avloppsvatten från tillverkning och i yt- och grundvatten är särskilt oroande, eftersom denna förekomst ökar den antimikrobiella resistensen (se kapitel 6). Läkemedel som finns i miljön påverkar inte bara miljön – om de kommer in i vattnets kretslopp eller i livsmedelskedjan påverkar de också människors hälsa direkt.

Sådana negativa effekter har beaktats i kommissionens nyligen antagna förslag till direktiv om rening av avloppsvatten från tätbebyggelse[48], som omfattar ett system för utökat producentansvar som även gäller läkemedel, och i kommissionens förslag till ändring av vattendirektiven[49] som tar upp läkemedel som finns i yt- och grundvatten.

Den föreslagna reformen av läkemedelslagstiftningen uppfyller ett antal åtaganden i strategin om läkemedel i miljön[50]. Den förbättrar miljöriskbedömningen av läkemedel för att säkerställa bättre utvärdering och begränsa deras potentiella negativa effekter på miljön och folkhälsan. I dag är miljöriskbedömningen obligatorisk för alla läkemedelsföretag som släpper ut läkemedel på EU-marknaden och omfattar användning och bortskaffande av läkemedel i miljön. I framtiden kommer arbetet med att främja EU:s miljöstandarder internationellt att fortsätta[51].

Förbättrad miljöriskbedömning inom ramen för godkännandet för försäljning

- Förbättra miljöriskbedömningen genom att införa en möjlighet att avslå godkännandet för försäljning om företagen inte lämnar tillräckliga bevis för att miljöriskbedömningen har genomförts eller om de föreslagna riskreducerande åtgärderna inte är tillräckliga för att motverka de fastställda riskerna.

[45] Meddelande från kommissionen, *Den europeiska gröna given*, COM(2019) 640 final.
[46] Meddelande från kommissionen, *Vägen till en frisk planet för alla. EU-handlingsplan: Med sikte på nollförorening av luft, vatten och mark*, COM(2021) 400 final.
[47] OECD: Pharmaceutical Residues in Freshwater Hazards and Policy Responses, 2019.
[48] Förslag till Europaparlamentets och rådets direktiv om rening av avloppsvatten från tätbebyggelse (omarbetning), COM (2022) 541 final.
[49] https://environment.ec.europa.eu/publications/proposal-amending-water-directives_sv
[50] Meddelande från kommissionen, *Europeiska unionens strategi om läkemedel i miljön*, COM(2019) 128 final.
[51] Mer information finns i avsnitt 7 i arbetsdokument från kommissionens avdelningar om sårbarheter i de globala leveranskedjorna för läkemedel, https://health.ec.europa.eu/system/files/2022-10/mp_vulnerabilities_global-supply_swd_en.pdf.

- Fastställa tydligare krav för miljöriskbedömningar, bland annat överensstämmelse med vetenskapliga riktlinjer, regelbundna uppdateringar av miljöriskbedömningen och skyldighet att göra ytterligare miljöriskbedömningar efter godkännandet.
- Utöka räckvidden för miljöriskbedömning till att omfatta risker för miljön från antibiotikatillverkning.
- Utvidga miljöriskbedömningen till alla produkter som redan finns på marknaden och som potentiellt kan vara skadliga för miljön.

För prövningsläkemedel som innehåller eller består av genetiskt modifierade organismer (GMO) inrättas genom reformen ett enda EU-förfarande för miljöriskbedömning för kliniska prövningar. En enda harmoniserad EU-omfattande bedömning kommer därmed att ersätta medlemsländernas bedömningar, vilket innebär att sponsorer av kliniska prövningar inte längre kommer att behöva lämna in flera ansökningar om godkännande. Dessutom kommer miljöriskbedömningens krav avseende bedömningen av läkemedel som innehåller eller består av genetiskt modifierade organismer att baseras på principerna i direktiv 2001/18/EG[52], men kommer att anpassas för att hänsyn ska tas till läkemedlens särdrag. Dessa förändringar innebär att betydande och tidskrävande rättsliga hinder avlägsnas, kliniska prövningar underlättas i EU och utvärdering och godkännande av innovativa, livräddande behandlingar optimeras.

6. Bekämpande av antimikrobiell resistens

Antimikrobiella medel[53] tillhör de viktigaste basläkemedlen. Med tiden har dock överanvändning och missbruk lett till en ökad antimikrobiell resistens, vilket i sin tur innebär att de blir ineffektiva och att infektioner blir allt svårare, om inte omöjliga, att behandla. Antimikrobiell resistens, som kallas ”den tysta pandemin”, orsakar varje år mer än 35 000 dödsfall i EU[54], och leder till höga kostnader för hälso- och sjukvårdssystemen[55]. Antimikrobiell resistens betraktas som en av de tre främsta hälsoriskerna i EU[56].

För att motverka den ökande antimikrobiella resistensen är det viktigt att säkerställa såväl tillgång till befintliga antimikrobiella medel som utveckling av nya effektiva sådana. För att undvika att mikroorganismer utvecklar resistens mot dessa antimikrobiella medel föreslås också åtgärder för återhållsam användning.

En begränsning av användningen av antimikrobiella medel har dock effekt på försäljningsvolymerna och på avkastningen på investeringarna för innehavare av godkännande för försäljning, vilket är orsaken till marknadsmisslyckandet. Därför behövs incitament för att utveckla innovativa antimikrobiella medel och säkra tillgången till dem.

[52] Europaparlamentets och rådets direktiv 2001/18/EG av den 12 mars 2001 om avsiktlig utsättning av genetiskt modifierade organismer i miljön och om upphävande av rådets direktiv 90/220/EEG (EGT L 106, 17.4.2001, s. 1).
[53] Antimikrobiella medel omfattar antibiotika, antivirala läkemedel, antimykotika och medel mot protozoer.
[54] https://www.ecdc.europa.eu/sites/default/files/documents/Health-burden-infections-antibiotic-resistant-bacteria.pdf.
[55] https://www.oecd.org/health/health-systems/AMR-Tackling-the-Burden-in-the-EU-OECD-ECDC-Briefing-Note-2019.pdf, 2019.
[56] De andra två prioriterade riskerna är enligt den bedömning som kommissionen gjort tillsammans med medlemsländerna patogener med hög pandemisk potential samt kemiska, biologiska, radiologiska och nukleära hot och risker (CBRN).

Utveckling av, tillgång till och återhållsam användning av antimikrobiella medel

Incitament för utveckling av och tillgång till antimikrobiella medel

EU behöver både push-incitament (dvs. finansiering av antimikrobiell forskning och innovation, främst genom forskningsbidrag och partnerskap) och pull-incitament (både rättsliga och finansiella) för att belöna framgångsrik utveckling av och säkra tillgången till effektiva antibakteriella medel. Kommissionen föreslår följande pull-incitament:

- Tillfälliga mekanismer som består av överförbara vouchers för dataexklusivitet, för utveckling av nya antimikrobiella medel, som ska tilldelas och användas på strikta villkor.
- Upphandlingsmekanismer för tillgång till nya och befintliga antimikrobiella medel som skulle garantera intäkter för innehavare av godkännande för försäljning av antimikrobiella medel, oavsett försäljningsvolymer.

EU måste snabbt hitta smarta sätt att utveckla nya antimikrobiella medel. Därför föreslås i reformen att man under 15 år ska testa ett system med överförbara vouchers för dataexklusivitet för nya antimikrobiella medel. Vouchern kommer att ge ett extra år med lagstadgat uppgiftsskydd[57] till utvecklaren av det antimikrobiella medlet. Utvecklaren kan använda den till någon av sina egna produkter eller sälja den till någon annan innehavare av godkännande för försäljning. Tillgången till systemet kommer att begränsas till banbrytande antimikrobiella medel som är inriktade på antimikrobiell resistens och de prioriterade patogener som erkänts av WHO. Användningen av vouchern kommer att styras av strikta villkor så att den främsta vinsten går till utvecklaren av det innovativa antimikrobiella medlet. Det föreslagna systemet omfattar också villkor för tillhandahållande av det antimikrobiella medlet som ska trygga leveransen av det när så krävs.

Ett vouchersystem skapar en attraktiv affärsnytta för utvecklingen av innovativa antimikrobiella medel för vilka den nuvarande forskningsplaneringen är mycket begränsad. Det här systemet kommer i slutändan att överföra kostnaderna för vouchrarna till medlemsländernas hälso- och sjukvårdssystem genom att fördröja marknadsinträdet för generiska läkemedel för de produkter som omfattas av vouchrarna. För att minska kostnaderna för hälso- och sjukvårdssystemen kommer reformen att begränsa antalet vouchrar som reserveras för nya antimikrobiella medel till högst tio vouchrar som kan beviljas under en period på 15 år. Om vouchrarna tillämpas på strikta villkor utgör de därför en trovärdig åtgärd mot antimikrobiell resistens eftersom nyttan och kostnaderna måste vägas mot kostnaden om inga åtgärder vidtas och den antimikrobiella resistensens påverkan på folkhälsan och ekonomin. Efter denna 15-årsperiod kommer vouchersystemet att utvärderas.

Förutom vouchersystemet skulle ekonomiska pull-incitament – i form av upphandlingsmekanismer – kunna införas. I en studie från kommissionen om att få ut medicinska motåtgärder mot antimikrobiell resistens på marknaden[58] bedömdes fyra viktiga typer av upphandlingsmekanismer som kan bidra till att öka de förväntade intäkterna för utvecklare: Intäktsgaranti, marknadsinträdesbelöning i kombination med intäktsgaranti, marknadsinträdesbelöning i form av ett engångsbelopp eller delmålsbetalningar. Med den årliga intäktsgarantimekanismen ”ökar” de offentliga myndigheterna intäkterna till utvecklare så att de når det ”garanterade” beloppet. Om försäljningen når upp till tröskelvärdet beviljas

[57] Begreppet lagstadgat uppgiftsskydd förklaras närmare i kapitel 4 i det här dokumentet.

[58] Europeiska kommissionen, Europeiska genomförandeorganet för hälsofrågor och digitala frågor, *Study on bringing AMR medical countermeasures to the market: final report*, Europeiska unionens publikationsbyrå, 2023, https://op.europa.eu/en/publication-detail/-/publication/51b2c82c-c21b-11ed-8912-01aa75ed71a1/language-en.

inget ytterligare belopp. Marknadsinträdesbelöningar består av ett antal betalningar till en utvecklare av antibiotika som lyckats få rättsligt godkännande för ett antibiotikum som uppfyller särskilda på förhand fastställda kriterier. Delmålsbelöningar är en ekonomisk belöning i ett tidigt skede då ett vissa forsknings- och utvecklingsmål har nåtts före marknadsgodkännandet (t.ex. att fas I har genomförts framgångsrikt). De här mekanismerna skulle i första hand ge tillgång till befintliga antimikrobiella medel, men de skulle också kunna stödja nya antimikrobiella medel i utvecklingsfasen. I den inledande förundersökningen fastställdes att alla alternativ kan genomföras som upphandlingstransaktioner – trots vissa betydande begränsningar och överväganden som kräver ytterligare djupgående undersökning. Det kommer förmodligen att krävas bidrag både från EU och från medlemsländerna.

Det finns ett stort behov av globalt stöd för utvecklingen av antimikrobiella medel. EU måste öka samarbetet genom befintliga forum, särskilt G7, G20, Transatlantiska arbetsgruppen om antibiotikaresistens, fyrpartsmötet med Världshälsoorganisationen, FN:s livsmedels- och jordbruksorganisation, Världsorganisationen för djurhälsa och FN:s miljöprogram, fonden Antimicrobial Resistance Multi-Partner Trust Fund, i förhandlingar om ett potentiellt internationellt avtal från Världshälsoorganisationen om förebyggande av samt beredskap och insatser vid pandemier[59] och med regionala institutioner som Afrikanska unionen.

Åtgärder för återhållsam användning av antimikrobiella medel

- Genom reformen av läkemedelslagstiftningen kommer åtgärder för återhållsam användning att bli en del av processen för godkännande för försäljning och omfatta förskrivning, lämplig förpackningsstorlek, specifik information för patienter/hälso- och sjukvårdspersonal, en strategi för antimikrobiell läkemedelsbehandling inbegripet riskreducerande åtgärder samt övervakning och rapportering av antimikrobiell resistens.
- Genom förslaget till rådets rekommendation kommer ytterligare stödåtgärder att föreslås, inbegripet rekommenderade mål och åtgärder för att främja omfattande åtgärder för förebyggande och kontroll av infektioner, förbättra medvetenheten och utbildningen och främja samarbete mellan berörda parter från alla relevanta sektorer.

Rekommenderade delmål för användning av antimikrobiella medel och för antimikrobiell resistens

Den föreslagna rådsrekommendationen ger konkreta mätbara delmål för att minska användningen av antimikrobiella medel och spridningen av antimikrobiell resistens hos människor. De här delmålen utformades med stöd av Europeiska centrumet för förebyggande och kontroll av sjukdomar och med beaktande av nationella situationer och de olika nivåerna av användning av antimikrobiella medel och av spridningen av viktiga läkemedelsresistenta mikroorganismer i medlemsstaterna. De tillåter riktat stöd och övervakning av framstegen under de kommande åren.

Andra rekommenderade åtgärder för att bekämpa antimikrobiell resistens

Den föreslagna rådsrekommendationen syftar också till att stärka de nationella One Health-handlingsplanerna mot antimikrobiell resistens, främja forskning och innovation, förstärka övervakningen och monitoreringen av antimikrobiell resistens och användningen av antimikrobiella medel, öka de globala åtgärderna och stimulera utveckling av andra medicinska motåtgärder mot antimikrobiell resistens, såsom vacciner och snabbtest, som

[59] https://www.who.int/news-room/questions-and-answers/item/pandemic-prevention--preparedness-and-response-accord.

också är avgörande. Den föreslagna rådsrekommendationen kommer också att bidra till en starkare ram för att bekämpa antimikrobiell resistens genom en kombination av en One Health-strategi och annan EU-politik, den gemensamma jordbrukspolitiken[60], från jord till bord-strategin[61], handlingsplanen för nollförorening av luft, vatten och mark[62], som syftar till att minska EU:s totala försäljning av antimikrobiella medel för produktionsdjur och i vattenbruk med 50 % till 2030, Horisont Europa[63] och de senaste kommissionsförslagen som ska leda till striktare miljöövervakning av antimikrobiell resistens[64].

7. Slutsats

Den föreslagna reformen av läkemedelslagstiftningen kommer att bana väg för ett starkare och mer resilient EU som bättre skyddar medborgarnas hälsa. Den kommer att främja snabb och lika tillgång till en kontinuerlig leverans av säkra, effektiva och prismässigt överkomliga läkemedel som tillgodoser patienternas medicinska behov i hela EU. Samtidigt kommer den att stimulera ytterligare innovation och stödja läkemedelsindustrins konkurrenskraft. Den kommer också att förbättra läkemedlens miljömässiga hållbarhet under hela deras livscykel.

Parallellt med detta kommer förslaget till rådets rekommendation om antimikrobiell resistens, tillsammans med de relaterade åtgärder som föreslås inom ramen för reformen av EU:s läkemedelslagstiftning, att komplettera och utvidga åtgärderna inom ramen för EU:s One Health-handlingsplan mot antimikrobiell resistens från 2017. Tillsammans kommer de att förse EU med de verktyg som behövs för att bekämpa denna tysta pandemi.

Det ambitiösa paket med förslag som ingår i reformen kommer att medföra varaktiga hälsomässiga, sociala, ekonomiska och miljömässiga fördelar för EU-medborgarna. Det kommer att stödja läkemedelsbranschens innovationskapacitet och konkurrenskraft i EU. Det kommer att bidra till att hantera globala utmaningar som antimikrobiell resistens och miljömässig hållbarhet och samtidigt stärka EU:s globala ledarskap på läkemedelsområdet, komplettera EU:s roll på det globala hälsoområdet och stödja genomförandet av EU:s globala hälsostrategi.

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[60] https://agriculture.ec.europa.eu/common-agricultural-policy/cap-overview/cap-glance_sv.

[61] Meddelande från kommissionen till Europaparlamentet, rådet, Europeiska ekonomiska och sociala kommittén samt Regionkommittén, *Från jord till bord-strategin för ett rättvisare, hälsosammare och miljövänligare livsmedelssystem*, COM(2020) 381 final.

[62] Meddelande från kommissionen till Europaparlamentet, rådet, Europeiska ekonomiska och sociala kommittén samt Regionkommittén, *Vägen till en frisk planet för alla – EU-handlingsplan: Med sikte på nollförorening av luft, vatten och mark*, COM(2021) 400 final.

[63] Europaparlamentets och rådets förordning (EU) 2021/695 av den 28 april 2021 om inrättande av Horisont Europa – ramprogrammet för forskning och innovation, om fastställande av dess regler för deltagande och spridning och om upphävande av förordningarna (EU) nr 1290/2013 och (EU) nr 1291/2013 (EUT L 170, 12.5.2021, s. 1).

[64] Kommissionens förslag av den 26 oktober 2022 till Europaparlamentets och rådets direktiv om ändring av direktiv 2000/60/EG om upprättande av en ram för gemenskapens åtgärder på vattenpolitikens område, direktiv 2006/118/EG om skydd för grundvatten mot föroreningar och försämring och direktiv 2008/105/EG om miljökvalitetsnormer inom vattenpolitikens område, COM(2022) 540 final 2022/0344 (COD), och kommissionens förslag av den 26 oktober 2022 till Europaparlamentets och rådets direktiv om rening av avloppsvatten från tätbebyggelse (omarbetning), COM(2022) 541 final, 2022/0345 (COD).

EUROPEAN
COMMISSION

Brussels, 26.4.2023
COM(2023) 192 final

2023/0132 (COD)

Proposal for a

DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

on the Union code relating to medicinal products for human use, and repealing Directive 2001/83/EC and Directive 2009/35/EC

(Text with EEA relevance)

{SEC(2023) 390 final} - {SWD(2023) 191 final} - {SWD(2023) 192 final} -
{SWD(2023) 193 final}

EXPLANATORY MEMORANDUM

1. CONTEXT OF THE PROPOSAL

• Reasons for and objectives of the proposal

EU pharmaceutical legislation has enabled the authorisation of safe, efficacious and high-quality medicinal products. However, patient access to medicinal products across the EU and security of supply are growing concerns, mirrored by recent Council conclusions[1] and resolutions of the European Parliament[2]. There is also a growing problem of shortages of medicinal products for many EU/EEA countries. Consequences of such shortages include decreased quality of treatment received by patients and increased burden on health systems and on healthcare professionals, who need to identify and provide alternative treatments. While the pharmaceutical legislation creates regulatory incentives for innovation and regulatory tools to support timely authorisation of innovative and promising therapies, these medicinal products do not always reach the patient, and patients in the EU have differing levels of access.

Moreover, innovation is not always focused on unmet medical needs, and there are market failures, especially in the development of priority antimicrobials that can help address antimicrobial resistance. Scientific and technological developments and digitalisation are not fully exploited, while the environmental impact of medicinal products needs attention. In addition, the authorisation system could be simplified to keep up with global regulatory competition. The pharmaceutical strategy for Europe[3] is a holistic answer to the current challenges of the pharmaceutical policy with legislative and non-legislative actions interacting together to achieve its overall goal of ensuring EU's supply of safe and affordable medicinal products and supporting the EU pharmaceutical industry's innovation efforts[4]. Reviewing the pharmaceutical legislation is key to achieving these objectives. However, innovation, access and affordability are also influenced by factors outside the scope of this legislation, such as global research and innovation activities or national pricing and reimbursement decisions. Hence, not all problems can be addressed by the reform of the legislation alone. Despite this, EU pharmaceutical legislation can be an enabling and connecting factor for innovation, access, affordability and environmental protection.

The proposed revision of the EU pharmaceutical legislation builds on the high level of public health protection and harmonisation already achieved for the authorisation of medicinal products. The overarching aim of the reform is to ensure that patients across the EU have timely and equitable access to medicines. Another objective of the proposal is to enhance security of supply and address shortages through specific measures, including stronger obligations on marketing authorisation holders to notify

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1 Council conclusions on strengthening the balance in the pharmaceutical systems in the EU and its Member States (OJ C 269, 23.07.2016, p. 31). Council conclusions on access to medicines and medical devices for a stronger and resilient EU, 2021/C 269 I/02 (OJ C 269I, 7.7.2021, p. 3).

2 European Parliament resolution of 2 March 2017 on EU options for improving access to medicine (2016/2057(INI), European Parliament resolution of 17 September 2020 on the shortage of medicines – how to address an emerging problem (2020/2071(INI).

3 Communication from the Commission, *Pharmaceutical Strategy for Europe* (COM/2020/761 final), https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe_en.

4 Mission letter of the President of the European Commission to Stella Kyriakides, Commissioner for Health and Food Safety, mission-letter-stella-kyriakides_en.pdf (europa.eu).

potential or actual shortages and marketing withdrawals, cessations and suspensions in advance of a foreseen interruption to continued supply of a medicinal product to the market. To support the sector's global competitiveness and innovative power, right balance needs to be struck between giving incentives for innovation, with more focus on unmet medical needs, and measures on access and affordability.

The framework needs to be simplified, adapted to scientific and technological changes, and contribute to reducing the environmental impact of medicinal products. This proposed reform is comprehensive but targeted and focuses on provisions relevant to achieving its specific objectives; therefore it covers all provisions apart from those concerning advertising, falsified medicinal products, and homeopathic and traditional herbal medicinal products.

Therefore, the objectives of the proposal are the following:

General objectives

– guarantee a high level of public health by ensuring the quality, safety and efficacy of medicinal products for EU patients;

– harmonise the internal market for the supervision and control of medicinal products and the rights and duties incumbent upon the competent authorities of the Member States.

Specific objectives

– make sure all patients across the EU have timely and equitable access to safe, effective, and affordable medicines.

– enhance security of supply and ensure medicines are always available to patients, regardless of where they live in the EU.

– offer an attractive, innovation-and competitiveness friendly environment for research, development, and production of medicines in Europe.

– make medicines more environmentally sustainable.

All the general and specific objectives set out above are also relevant for the areas of medicinal products for rare diseases and for children.

• **Consistency with existing provisions in the policy area**

The current EU pharmaceutical legislation includes both general and specific legislation. Directive 2001/83/EC of the European Parliament and of the Council[5] and Regulation (EC) No 726/2004 of the European Parliament and of the Council[6] (together 'general pharmaceutical legislation') lay down provisions related to medicinal products authorisation and post-authorisation requirements, pre-authorisation support schemes, regulatory incentives in terms of data and market protection, manufacturing and supply, and the European Medicines Agency (EMA). The general pharmaceutical legislation is complemented by specific legislation on medicinal products for rare diseases (Regulation (EC) No 141/2000, the 'Orphan

5 Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, p. 67).

6 Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ L 136, 30.4.2004, p. 1).

Regulation'[7]), medicinal products for children (Regulation (EC) No 1901/2006, the 'Paediatric Regulation'[8]) and advanced therapy medicinal products (Regulation (EC) No 1394/2007, the 'ATMP Regulation'[9]).The proposed revision of the pharmaceutical legislation will consist of two legislative proposals:

– a new directive, repealing and replacing Directive 2001/83/EC and Directive 2009/35/EC of the European Parliament and of the Council[10] and incorporating relevant parts of the Paediatric Regulation (Regulation (EC) No 1901/2006);

– a new regulation, repealing and replacing Regulation (EC) No 726/2004, repealing and replacing the Orphan Regulation (Regulation (EC) No 141/2000) and repealing and incorporating relevant parts of the Paediatric Regulation (Regulation (EC) No 1901/2006).

The merger of the Orphan Regulation and the Paediatric Regulation with the legislation applicable to all medicinal products will allow for simplification and increased coherence.

Medicinal products for rare diseases and for children will continue to fall under the same provisions as any other medicinal product concerning their quality, safety and efficacy, for example concerning the marketing authorisation procedures, pharmacovigilance and quality requirements. However, specific requirements will also continue to apply to these types of medicinal products in order to support their development. This is because market forces alone have proven insufficient to stimulate adequate research and development of medicinal products for children and patients suffering from a rare disease. Such requirements, which are currently laid down in separate legislative acts, should be integrated into the regulation and this directive in order to ensure clarity and coherence of all the measures applicable to these medicinal products.

• **Consistency with other Union policies**

The EU pharmaceutical legislation described above has close links with several other related pieces of EU legislation. The 'Clinical Trials Regulation' (Regulation (EU) No 536/2014)[11] allows for more efficient approval of clinical trials in the EU. Regulation (EU) 2022/123[12] strengthens the role of the European Medicines Agency in order to facilitate a coordinated EU-level response to health crises. The EMA fees

7 Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products (OJ L 18, 22.1.2000, p. 1).

8 Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 (OJ L 378, 27.12.2006, p. 1).

9 Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (OJ L 324, 10.12.2007, p. 121).

10 Directive 2009/35/EC of the European Parliament and of the Council of 23 April 2009 on the colouring matters which may be added to medicinal products (OJ L 109, 30.4.2009, p. 10).

11 Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (OJ L 158, 27.5.2014, p. 1).

12 Regulation (EU) 2022/123 of the European Parliament and of the Council of 25 January 2022 on a reinforced role for the European Medicines Agency in crisis preparedness and management for medicinal products and medical devices (OJ L 20, 31.1.2022, p. 1).

legislation[13] contributes to providing adequate financing for the EMA's activities, including respective remuneration to national competent authorities for their contribution to completing the EMA's tasks.

There are also links with EU regulatory frameworks for other health products. EU legislation on blood, tissues and cells (BTC)[14] is relevant, as some substances of human origin are starting materials for medicinal products. The EU regulatory framework for medical devices[15] is also relevant, as there are products that combine medicinal products and medical devices.

Futhermore, the objectives of the proposed reform of the pharmaceutical legislation are consistent with those of a number of broader EU policy agendas and initiatives.

In terms of promoting innovation, Horizon Europe[16], a key funding programme for EU research and innovation, and Beating Cancer Plan[17] both support research and development of new medicinal products. In addition, innovation in the pharmaceutical sector is promoted by the intellectual property frameworks, on patents under the national patent laws, the European Patent Convention and the Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement, and on supplementary protection certificates under the EU SPC Regulation[18]. The intellectual property action plan[19] under the Industrial Strategy includes modernising the system of supplementary protection certificates (SPCs). SPCs extend certain patent rights to protect innovation and compensate for lengthy clinical trials and marketing authorisation procedures. With regard to addressing unmet medical needs in the area of antimicrobial resistance, the proposed reform of the pharmaceutical legislation will contribute to the objectives of the European one health action plan against antimicrobial resistance (AMR)[20].

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13 Council Regulation (EC) No 297/95 of 10 February 1995 on fees payable to the European Agency for the Evaluation of Medicinal Products, and Regulation (EU) No 658/2014 of the European Parliament and of the Council on fees payable to the European Medicines Agency for the conduct of pharmacovigilance activities in respect of medicinal products for human use (OJ L 35, 15.2.1995, p. 1).

14 Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC, and Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells (OJ L 033, 8.2.2003, p. 30).

15 Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (OJ L 117, 5.5.2017, p. 1) and Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU (OJ L 117, 5.5.2017, p. 176).

16 Regulation (EU) 2021/695 of the European Parliament and of the Council of 28 April 2021 establishing Horizon Europe – the Framework Programme for Research and Innovation, laying down its rules for participation and dissemination, and repealing Regulations (EU) No 1290/2013 and (EU) No 1291/2013 (OJ L 170, 12.5.2021, p. 1).

17 Communication from the Commission, *Europe's Beating Cancer Plan* (COM/2021/44 final).

18 Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the supplementary protection certificate for medicinal products (OJ L 152, 16.6.2009, p. 1).

19 Communication from the Commission, *Making the most of the EU's innovative potential. An intellectual property action plan to support the EU's recovery and resilience* (COM/2020/760 final).

20 Communication from the Commission, *A European One Health Action Plan against Antimicrobial Resistance (AMR)*, https://ec.europa.eu/health/system/files/2020-01/amr_2017_action-plan_0.pdf.

Concerning access to medicinal products, in addition to the pharmaceutical legislation, the intellectual property frameworks, the Health Technology Assessment (HTA) Regulation (Regulation (EU) 2021/2282, the 'HTA Regulation')[21] and the Transparency Directive (Directive 89/105/EEC)[22] also play a role. In addition to extending certain patent rights to protect innovation, SPCs impact the effect of regulatory protection periods provided by the pharmaceutical legislation and therefore the entry of generic and biosimilar medicinal products and ultimately patient access to medicinal products and affordability. Under the HTA Regulation, national HTA bodies will conduct joint clinical assessments that compare new medicinal products to existing ones. Such joint clinical assessments will help Member States take more timely and evidence-based decisions on pricing and reimbursement. Finally, the Transparency Directive regulates procedural aspects of the Member States' pricing and reimbursement decisions but does not effect the level of price.

In order to enhance security of supply of medicinal products, the proposed reform of the pharmaceutical legislation aims to address systemic shortages and supply chain challenges. The proposed reform therefore complements and further develops the roles of the Member States and competent authorities of the Member States as set out in the extension of the EMA mandate (Regulation (EU) 2022/123), and is aimed at ensuring access to and continued supply of critical medicinal products during health crises. It also complements the mission of the Health Emergency Preparedness and Response Authority (HERA) to ensure availability of medical countermeasures in preparation for and during health crises. The proposed reform of the pharmaceutical legislation is therefore consistent with the package of legislative initiatives related to health security under the European Health Union[23].

To address environmental challenges, the proposed reform of the pharmaceutical legislation will support initiatives under the European Green Deal[24]. These include the EU action plan 'Towards Zero Pollution for Air, Water and Soil' and the revision of: (i) the Urban Waste Water Treatment Directive[25], (ii) the Industrial Emissions Directive[26] and (iii) the list of surface and groundwater pollutants under the Water Framework Directive[27]. The proposal is also well aligned with the Strategic Approach to Pharmaceuticals in the Environment[28].

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21 Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU (OJ L 458, 22.12.2021, p. 1).

22 Council Directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of national health insurance systems (OJ L 40, 11.2.1989, p. 8).

23 European Health Union - Protecting the health of Europeans and collectively responding to cross-border health crises, https://commission.europa.eu/strategy-and-policy/priorities-2019-2024/promoting-our-european-way-life/european-health-union_en.

24 Communication from the Commission, *The European Green Deal* (COM/2019/640 final).

25 Council Directive 91/271/EEC of 21 May 1991 concerning urban waste-water treatment (OJ L 135, 30.5.1991, p. 40).

26 Directive 2010/75/EU of the European Parliament and of the Council of 24 November 2010 on industrial emissions (integrated pollution prevention and control) (OJ L 334 17.12.2010, p. 17).

27 Directive 2000/60/EC of the European Parliament and of the Council of 23 October 2000 establishing a framework for Community action in the field of water policy (OJ L 327, 22.12.2000, p. 1) and Directive 2013/39/EU of the European Parliament and of the Council of 12 August 2013 amending Directives

Finally, on the use of health data, the European Health Data Space[29] will provide a common framework across Member States for access to high-quality real world health data. This will promote progress in research and development of medicinal products and provide new tools for pharmacovigilance and comparative clinical assessments. By facilitating access to and use of health data, the two initiatives together will support the competitiveness and innovation capacity of the EU's pharmaceutical industry.

2. LEGAL BASIS, SUBSIDIARITY AND PROPORTIONALITY

- **Legal basis**

The proposal is based on Articles 114(1) and 168(4), point (c) of the Treaty on the Functioning of the European Union (TFEU). This is consistent with the legal basis of existing EU pharmaceutical legislation. Article 114(1) has as its object the establishment and functioning of the internal market, while Article 168(4), point (c) relates to the setting of high standards for the quality and safety of medicinal products.

- **Subsidiarity (for non-exclusive competence)**

Common standards of quality, safety and efficacy for the authorisation of medicinal products constitute a cross-border public health issue that affects all Member States and thus can be regulated effectively only at EU level. EU action relies also on the single market to achieve a stronger impact as regards access to safe, effective and affordable medicinal products, and with regard to the security of supply across the EU. Uncoordinated measures by Member States may result in distortions of competition and barriers to intra-EU trade for medicinal products that are relevant for the entire EU, and would also likely increase administrative burden for pharmaceutical companies, which often operate in more than one Member State.

A harmonised approach at EU level also provides greater potential for incentives to support innovation and for concerted action to develop medicinal products in areas of unmet medical needs. Moreover, simplification and streamlining of processes under the proposed reform are expected to reduce administrative burden for companies and authorities and hence improve the efficiency and attractiveness of the EU system. The reform will also have a positive influence on the competitive functioning of the market through targeted incentives and other measures that facilitate early market entry of generic and biosimilar medicinal products, contributing to patient access and affordability. Nevertheless, the proposed reform of the pharmaceutical legislation respects Member States' exclusive competence in the provision of health services, including pricing and reimbursement policies and decisions.

2000/60/EC and 2008/105/EC as regards priority substances in the field of water policy Text with EEA relevance (OJ L 226, 24.8.2013, p. 1).

[28] Strategic Approach to Pharmaceuticals in the Environment, https://ec.europa.eu/environment/water/water-dangersub/pharmaceuticals.htm.

[29] Communication from the Commission, *A European Health Data Space: harnessing the power of health data for people, patients and innovation* (COM/2022/196 final).

- **Proportionality**

The initiative does not go beyond what is necessary to achieve the objectives of the reform. It does so in a way that is conducive to national action, which would otherwise not be sufficient to achieve those objectives in a satisfactory way.

The principle of proportionality has been reflected in the comparison of different options evaluated in the impact assessment. For example, trade-offs are inherent between the objective of innovation (promoting the development of new medicinal products) and the objective of affordability (which is often achieved by generic/biosimilar competition). The reform maintains the incentives as a key element for innovation, but they are adapted to better encourage and reward product development in areas of unmet medical needs and to better address timely patient access to medicinal products in all Member States.

- **Choice of the instrument**

The proposed directive introduces a large number of amendments to Directive 2001/83/EC and incorporates part of the current provisions and amendments to Regulation (EC) No 1901/2006. A new directive repealing Directive 2001/83/EC (rather than an amending directive) is therefore considered the appropriate legal instrument. A directive remains the best choice of legal instrument to avoid fragmentation of national legislation on medicinal products for human use, given that the legislation is based on a system of national and EU marketing authorisations. National authorisations are granted and managed on the basis of national laws implementing the EU law. The evaluation of the general pharmaceutical legislation has not found that the choice of legal instrument has caused specific problems or reduced the level of harmonisation. In addition, a REFIT Platform opinion[30] from 2019 showed that there was no support among the Member States to turn Directive 2001/83/EC into a regulation.

3. RESULTS OF EX-POST EVALUATIONS, STAKEHOLDER CONSULTATIONS AND IMPACT ASSESSMENTS

- **Ex-post evaluations/fitness checks of existing legislation**

For the reform of the general pharmaceutical legislation, stakeholder consultation activities were carried out as part of 'back-to-back' evaluations and impact assessments of the general pharmaceutical legislation and of the Orphan and Paediatric Regulations[31].

For medicinal products for rare diseases and for children a joint evaluation on the functioning of the two pieces of legislation was carried out and published in 2020[32].

For the general pharmaceutical legislation the evaluation of the legislation showed that the legislation continues to be relevant for the dual overarching objectives of protecting public health and harmonising the internal market for medicinal products in the EU. The legislation delivered on the objectives of the 2004 revision, albeit not

30 The EU's efforts to simplify legislation – 2019 Annual Burden survey, https://commission.europa.eu/system/files/2020-08/annual_burden_survey_2019_4_digital.pdf.

31 Commission staff working document, Impact Assessment, Annex 5: Evaluation.

32 Evaluation of the medicines for rare diseases and children legislation, https://health.ec.europa.eu/medicinal-products/medicines-children/evaluation-medicines-rare-diseases-and-children-legislation_en.

to the same extent for all. The objective of ensuring quality, safety and efficacy of medicinal products was achieved to the largest extent, while patient access to medicinal products in all Member States was achieved only to a limited extent. As to ensuring the competitive functioning of the internal market and attractiveness in a global context, the legislation has performed to a moderate extent. The evaluation found that the achievements or shortcomings of the 2004 revision vis-a-vis its objectives depend on many external factors outside the remit of the legislation. These include R&D activities and international location of R&D clusters, national pricing and reimbursement decisions, business decisions and market size. The pharmaceutical sector and the development of medicinal products are global; research and clinical trials conducted on one continent will support development and authorisation in other continents; global are also the supply chains and manufacturing of medicinal products. International cooperation to harmonise requirements to support authorisation exists, e.g. the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use[33].

The evaluation identified the main shortcomings that the pharmaceutical legislation has not adequately addressed, while recognising that these also depend on factors outside its remit. These main shortcomings are as follows:

– Medical needs of patients are not sufficiently met.

– Affordability of medicinal products is a challenge for health systems.

– Patients have unequal access to medicinal products across the EU.

– Shortages of medicinal products are an increasing problem in the EU.

– The medicinal product lifecycle can have negative impacts on the environment.

– The regulatory system does not sufficiently cater for innovation and in some instances creates unnecessary administrative burden.

Concerning medicinal products for rare diseases and for children, the evaluation showed that overall the two specific pieces of legislation have achieved positive results by allowing more medicinal products to be developed for these two population groups. However, it also identified important shortcomings, which are similar to the ones identified for the general pharmaceutical legislation:

– Medical needs of patients with rare diseases and of children are not sufficiently met.

– Affordability of medicinal products is a growing challenge for health systems.

– Patients have unequal access to medicinal products across the EU.

– The regulatory system does not sufficiently cater for innovation and in some instances creates unnecessary administrative burden.

- **Stakeholder consultations**

For the reform of the general pharmaceutical legislation, stakeholder consultation activities were carried out as part of the 'back-to-back' evaluation and impact assessment[34]. A single consultation strategy was prepared for this exercise, including

[33] ICH – harmonisation for better health, https://www.ich.org/.

[34] Commission staff working document, Impact Assessment, Annex 2: Stakeholder Consultation (Synopsis Report).

consultation activities looking backward and forward. It aimed to collect inputs and perspectives of all stakeholder groups both on the evaluation of the legislation and for the impact assessment of different possible policy options for the reform.

The following key stakeholder groups were identified as priority groups in the consultation strategy: the public; organisations representing patients, consumers and civil society active in public health and social issues ('CSOs'); healthcare professionals and healthcare providers; researchers, academia and learned societies (academics); environmental organisations; the pharmaceutical industry and their representatives.

As part of the internal policy work process supporting the revision, the Commission collaborated with the European Medicines Agency (EMA) and the competent authorities of the Member States (NCAs) dealing with the regulation of medicinal products. Both actors play a pivotal role in implementing the pharmaceutical legislation.

Information was collected through consultations that took place between 30 March 2021 and 25 April 2022. These consisted of:

– feedback on the Commission's combined evaluation roadmap/inception impact assessment (30 March-27 April 2021);

– Commission online public consultation (28 September - 21 December 2021);

– targeted stakeholder surveys with public authorities, the pharmaceutical industry including SMEs, academia, civil society representatives and healthcare providers (survey) (16 November 2021-14 January 2022);

– interviews (2 December 2021-31 January 2022);

– a validation workshop on the evaluation findings (workshop 1) on 19 January 2022;

– a validation workshop on the impact assessment findings (workshop 2) on 25 April 2022.

There was broad consensus among stakeholders that the current pharmaceutical system guarantees a high level of patient safety on which the revision can build to address new challenges and improve supply of safe and affordable medicinal products, patient access and innovation, especially in areas where the medical needs of patients are not met. The public, patients and civil society organisations expressed their expectation of equitable access to innovative therapies across the EU, including for unmet medical needs, and continuous supply of their medicinal products. Public authorities and patient organisations opted for a variable duration for the current main incentives, as reflected in the preferred option. The pharmaceutical industry argued against any introduction of variable incentives or the shortening of existing ones and favoured the introduction of additional or novel incentives. Industry also highlighted the need for stability in the current legal framework and predictability for incentives. The elements on the environment, regulatory support for non-commercial entities and repurposing of medicinal products included in the preferred option were supported by key stakeholders such as healthcare providers, academia and environmental organisations.

Concerning the revision of the legislation on medicinal products for children and for rare diseases, specific consultation activities were carried out in the context of the impact assessment procedure: a public consultation ran from 7 May to 30 July 2021.

Furthermore, targeted surveys, including a costing survey both for pharmaceutical companies and public authorities, were conducted from 21 June to 30 July 2021 (late responses were accepted until the end of September 2021, due to the summer break). An interview programme with all relevant stakeholder groups (public authorities, pharmaceutical industry including SMEs, academia, civil society representatives and healthcare providers) was conducted at the end of June 2021, while focus groups met on 23 February 2022 to discuss some of the main issue of the reform.

There was broad consensus among stakeholders that the two pieces of legislation have had a positive effect on the development of medicinal products for children and the treatment of rare diseases. However, concerning the Paediatric Regulation, all the current structure of the paediatric investigation plan and of the condition allowing the waiver of the obligation to draw up such a plan were considered as possible obstacles to the development of certain innovative products. All stakeholders highlighted that for both the medicinal products for rare diseases and the medicinal products for children, medicinal products addressing unmet medical needs of patients should be better supported. Public authorities supported a variable duration for market exclusivity for medicinal products for rare diseases as a tool to better focus development in areas where treatments are not available. The pharmaceutical industry argued against any introduction of variable incentives or the shortening of existing ones and favoured the introduction of additional or novel incentives. As for the revision of the general pharmaceutical legislation, industry also highlighted the need for stability in the current legal framework and predictability for incentives.

- **Collection and use of expertise**

In addition to the extensive stakeholder consultation described in previous sections, the following external studies were conducted to support the 'back-to-back' evaluation and impact assessment of the general pharmaceutical legislation and the evaluation and impact assessment of the orphan and paediatric legislation:

– *Study supporting the Evaluation and Impact Assessment of the general pharmaceutical legislation. Evaluation Report*, Technopolis Group (2022).

– *Study supporting the Evaluation and Impact Assessment of the general pharmaceutical legislation. Impact Assessment Report*, Technopolis Group (2022).

– *Future-proofing pharmaceutical legislation - Study on medicine shortages*, Technopolis Group (2021).

– *Study to support the evaluation of the EU Orphan Regulation*, Technopolis Group and Ecorys (2019).

– *Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe*, Copenhagen Economics (2018).

– *Study on the economic impact of the Paediatric Regulation, including its rewards and incentives*, Technopolis Group and Ecorys (2016).

- **Impact assessments**

General pharmaceutical legislation

The impact assessment for the revision of the general pharmaceutical legislation[35] analysed three policy options (A, B and C).

– Option A builds on the status quo and achieves the objectives mainly through new incentives.

– Option B reaches the objectives through more obligations and oversight.

– Option C adopts a 'quid pro quo' approach in the sense that positive behaviour is rewarded and obligations are only used when there are no alternatives.

Option A maintains the current system of regulatory protection for innovative medicinal products and adds additional conditional periods of protection. Priority antimicrobials benefit from a transferable exclusivity voucher. Current requirements on security of supply are retained (notification of withdrawal at least two months in advance). The existing requirements on the environmental risk assessment continue with additional information obligations.

Option B provides for a variable duration of regulatory data protection periods (split into standard and conditional periods). Companies must either have an antimicrobial in their portfolio or pay into a fund to finance the development of new ones. Companies are obliged to launch medicinal products with an EU-wide authorisation in the majority of Member States (small markets included) and to provide information on public funding received. Current requirements on security of supply are retained and companies are obliged to offer their marketing authorisation for transfer to another company before withdrawal. The environmental risk assessment results in additional responsibilities for companies.

Option C provides for a variable duration of regulatory data protection (split into standard and conditional periods), striking a balance between providing attractive incentives for innovation and supporting timely patient access to medicinal products across the EU. Priority antimicrobials can benefit from a transferable exclusivity voucher subject to strict eligibility criteria and conditions for use of the voucher, while prudent-use measures further contribute to addressing antimicrobial resistance. Marketing authorisation holders are required to ensure transparency on public funding for clinical trials. Reporting of shortages is harmonised and only critical shortages are brought to the attention of authorities at the EU level. Marketing authorisation holders are obliged to notify possible shortages earlier and to offer their marketing authorisation for transfer to another company before withdrawal. Requirements on the environmental risk assessment and conditions of use are strengthened.

All options are complemented by a set of common elements aimed at simplifying and streamlining regulatory procedures and future-proofing the legislation with a view to accommodating novel technologies.

The preferred option is based on option C and also includes the common elements mentioned above. The preferred option was considered to be the best policy choice, taking into account the specific objectives of the revision and the economic, social and environmental impacts of the proposed measures.

The preferred option and its introduction of variable incentives is a cost-effective way of achieving the objectives of improved access, addressing unmet medical need

[35] Commission staff working document, Impact Assessment.

and affordability for health systems. It is expected to provide 15% increased access, meaning 67 million more people residing in the EU who can potentially benefit from a new medicinal product, and more medicinal products addressing unmet medical needs at the same cost for the public payers as today. In addition, savings are expected for companies and regulatory authorities through the cross-cutting measures that would allow for better coordination, simplification and accelerated regulatory processes.

Measures to incentivise the development of priority antimicrobials are estimated to entail costs for public payers and the generic industry but could be effective against antimicrobial resistance if applied under strict conditions and with tight measures for prudent use. These costs must also be seen in the context of the threat of resistant bacteria and current costs incurred from antimicrobial resistance including deaths, healthcare costs and productivity losses.

The originator companies would have additional costs and benefits from the incentives and the market launch conditionality, and overall they would see an increase in their sales. Some increased costs will be associated with the reporting on shortages. Regulatory authorities will incur costs to perform additional tasks in the areas of shortage management, strengthened environmental risk assessment and enhanced pre-authorisation scientific and regulatory support.

Orphan and paediatric legislation

The impact assessment on the revision of the *orphan* and *paediatric* legislation also analysed three policy options (A, B and C) per legislative act. The different policy options vary as to the incentives or rewards to which medicinal products for rare diseases and for children would be entitled. In addition, the revision will include a series of common elements present in all options.

For medicinal products for *rare diseases*, option A keeps the 10 years of market exclusivity and adds - as an additional incentive - a transferable regulatory protection voucher for products addressing a high unmet medical need (HUMN) of patients. Such a voucher allows for a one-year extension in the length of regulatory protection or can be sold to another company and used for a product in that company's portfolio.

Option B abolishes the current market exclusivity of 10 years for all orphan medicinal products.

Option C provides for a variable duration of market exclusivity of 10, 9 and 5 years, based on the type of orphan medicinal product (for HUMN, new active substances and well-established use applications respectively). A 'bonus' market exclusivity extension of one year can be granted, based on patient accessibility in all relevant Member States, but only for HUMN products and new active substances.

All options are complemented by a set of common elements aimed at simplifying and streamlining regulatory procedures and future-proofing the legislation.

Option C was considered to be the best policy choice, taking into account the specific objectives and the economic and social impacts of the proposed measures. This option is expected to provide a balanced positive outcome contributing to the achievement of the four objectives of the revision. It will aim to refocus investments and boost innovation, in particular in products addressing HUMN, without undermining the development of other medicinal products for rare diseases. The measures provided for under this option are also expected to improve the

competitiveness of EU pharmaceutical industry, including of SMEs, and will lead to the best results in terms of patient access (due to: (i) the possibility for generics and biosimilars to enter the market earlier than they do today; and (ii) the proposed access conditionality for extending the market exclusivity). Furthermore, more flexible criteria to better define an orphan condition will make the legislation more 'fit' to accommodate new technologies and reduce administrative burdens.

The total balance of yearly costs and benefit calculated per interested stakeholder group for this preferred option compared to the baseline are: EUR 662 million cost savings for public payers from accelerated generic entry and a EUR 88 million profit gain for the generic industry. The public will benefit from an additional one or two HUMN medicinal products and overall broader and faster access for patients. Originators will see an estimated EUR 640 million gross profit loss from earlier generic entry, but savings are expected for companies through the cross-cutting measures in the general pharmaceutical legislation that would allow for better coordination, simplification and accelerated regulatory processes.

For medicinal products *for children*, in option A the six month supplementary protection certificate (SPC) extension is kept as a reward for all medicinal products completing a paediatric investigation plan ('PIP'). Furthermore, an extra reward benefiting products addressing unmet medical needs of children is added. This will consist of either 12 extra months of SPC extension or a regulatory protection voucher (duration one year), which could be transferred to another product (possibly of another company) against payment, allowing the receiving product to benefit from extended regulatory data protection (+one year). In option B, the reward for completing a PIP is abolished. Developers of every new medicinal product would continue to be obliged to agree with the EMA and conduct a PIP, but the extra costs incurred would not be rewarded. In option C, like today, the six month SPC extension remains the main reward for completing a PIP. All options are complemented by a set of common elements aimed at simplifying and streamlining regulatory procedures and future-proofing the legislation.

Option C was considered the best policy choice, taking into account the proposed measures' specific objectives and economics and social impacts. Option C is expected to yield to an increased number of medicinal products, in particular in areas of unmet medical needs of children, which are expected to reach children faster than today. It would also ensure a fair return of investment for medicinal products developers who fulfil the legal obligation to study medicinal products in children, as well as reduced administrative costs linked to the procedures that follow from the obligation.

New simplification measures and obligations (for example those linked to medicinal product's mechanism of action) are expected to cut time to access to children's versions of medicinal products by 2-3 years and to bring three more new medicinal products for children yearly compared to the baseline, which in turn results in additional rewards for developers. These new medicinal products for children will result, on a yearly basis, in costs for the public estimated EUR 151 million, while originator companies would gain EUR 103 million in gross profits to compensate their efforts. Thanks to simplification of the rewards scheme linked to the study of medicinal products for use in children, generic companies will find it easier to predict when they will be able to enter the market.

- **Regulatory fitness and simplification**

  The proposed revisions aim to simplify the regulatory framework and improve its effectiveness and efficiency, thereby reducing the administrative costs borne by companies and competent authorities. Most of the envisaged measures will act on core procedures for the authorisation and lifecycle management of medicinal products.

  Administrative costs will fall for competent authorities, business and other relevant entities, for two overarching reasons. Firstly, procedures will be streamlined and accelerated, for example in connection with the renewal of marketing authorisations and the submission of variations or the transfer of the responsibility for orphan designations from the Commission to the EMA. Secondly, there will be enhanced coordination of the European medicines regulatory network, for example in terms of the work of different EMA committees and interactions with related regulatory frameworks. Further contributions to cost reductions for business and administrations are expected to come from adaptations to accommodate new concepts such as adaptive clinical trials, a medicinal product's mechanism of action, use of real world evidence, and new uses of health data within the regulatory framework.

  Enhanced digitisation will facilitate the integration of regulatory systems and platforms across the EU and support for the re-use of data, and is expected to reduce costs for administrations over time (although it may induce initial one-off costs). For example, electronic submissions by industry to the European Medicines Agency and competent authorities of the Member States will deliver cost savings to industry. Moreover, the envisaged use of the electronic product information (as opposed to paper leaflets) should also lead to administrative cost reductions.

  SMEs and non-commercial entities involved in the development of medicinal products are expected to benefit in particular from the envisaged simplification of procedures, wider use of electronic processes and reduction of administrative burden. The proposal also aims at optimising the regulatory support (e.g. scientific advice) to SMEs and non-commercial organisations, resulting in additional reductions of administrative costs for these parties.

  Overall, the envisaged measures for simplification and burden reduction are expected to reduce costs for businesses, supporting the 'one in one out' approach. In particular, the proposed streamlining procedures and enhanced support are expected to yield cost savings for EU pharmaceutical industry.

- **Fundamental rights**

  The proposal contributes to achieving a high level of human health protection and is therefore consistent with Article 35 of the Charter of Fundamental Rights of the European Union.

4. BUDGETARY IMPLICATIONS

The financial impact is shown in the Legal Financial Statement attached to the proposal for a Regulation of the European Parliament and of the Council, laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, amending Regulation (EC) No 1394/2007 and Regulation (EU) No 536/2014 and repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006.

5. OTHER ELEMENTS

- **Implementation plans and monitoring, evaluation and reporting arrangements**

  The development of new medicinal products can be a long process that can take up to 10-15 years. Incentives and rewards therefore have an influence many years after the marketing authorisation date. The benefit for patients also needs to be measured over a period of at least 5-10 years after a medicinal product is authorised. The Commission intends to monitor relevant parameters that enable assessment of progress of the proposed measures with a view to reaching their objectives. The majority of indicators are already collected at the EMA level. Furthermore, the Pharmaceutical Committee[36] will provide a forum for discussing issues related to the transposition and monitoring progress. The Commission will report on the monitoring periodically. A meaningful evaluation of the results of the revised legislation can only be envisaged after at least 15 years from the deadline for its transposition.

- **Explanatory documents (for directives)**

  Following the ruling of the European Court of Justice in Commission vs Belgium (Case C-543/17), Member States must accompany their notifications of national transposition measures with sufficiently clear and precise information, indicating which provisions of national law transpose which provisions of a directive. This must be provided for each obligation, not only at article level. If Member States comply with this obligation, they would not need, in principle, to send explanatory documents on the transposition to the Commission.

- **Detailed explanation of the specific provisions of the proposal**

  The proposed revision of the pharmaceutical legislation consists of a proposal for a new directive and a proposal for a new regulation (see previous section 'Consistency with existing provisions in the policy area'), which will also cover orphan and paediatric medicinal products. Provisions for orphan medicinal products have been integrated in the proposed regulation. While procedural requirements applicable to paediatric medicinal products are primarily integrated in the new regulation, the general framework for the authorisation and rewarding of these products have been included in the new directive. The main areas of the revision under the proposed new regulation are covered by the explanatory memorandum of the accompanying proposal for a regulation.

  Annex II to the directive contains the existing text of Annex I. Annex II will be updated by delegated act. The delegated act will be adopted and applied before the deadline for the transposition of the directive.

  The proposed directive includes the following main areas of revision:

  Promoting innovation and access to affordable medicinal products - creating a balanced pharmaceutical ecosystem

  To enable innovation and promote the competitiveness of the EU pharmaceutical industry, in particular SMEs, the provisions of the proposed directive work in synergy with those of the proposed regulation. In this respect, a balanced system of incentives is proposed. The system rewards innovation, especially in areas of unmet

[36] Council Decision of 20 May 1975 setting up a pharmaceutical committee (75/320/EEC).

medical needs, and innovation reaches patients and improves access across the EU. To make the regulatory system more efficient and innovation-friendly, measures are proposed to simplify and streamline procedures and to create an agile and future-proof framework (see also measures under 'Reducing regulatory burden and providing a flexible regulatory framework to support innovation and competitiveness' below and in the proposed regulation).

Introduction of variable incentives related to regulatory data protection and rewarding of innovation in areas of unmet medical needs

The current standard period of regulatory data protection will be reduced from eight years to six years. Nevertheless, this remains competitive given what other regions offer. Furthermore, marketing authorisation holders will benefit from additional periods of data protection (beyond the standard six years) if they launch the medicinal products in all Member States covered by the marketing authorisation (+two years), if they address unmet medical needs (+six months), if they conduct comparative clinical trials (+six months) or for an additional therapeutic indication (+ one year).

Prolongation of data protection for the market launch will be granted if the medicinal product is supplied in accordance with the needs of the Member States concerned within two years from the marketing authorisation (or within three years in the case of SMEs, not-for-profit entities or companies with limited experience in the EU system). Member States have the possibility to waive the condition of launch in their territory for the purpose of the prolongation. This is expected to be the case particularly in situations where launch in a particular Member State is materially impossible or because there are special reasons why a Member State wishes that launch takes place later. Such a waiver does not mean that a Member State is not interested in the medicinal product altogether.

Prolongation of data protection for addressing unmet medical need will be granted if the medicinal product is for a life-threatening or seriously debilitating disease with remaining high morbidity or mortality, and the use of the medicinal product results in a meaningful reduction in disease morbidity or mortality. The various elements of this criterion-based definition of unmet medical need (e.g. "remaining high morbidity or mortality") will be further specified in implementing acts, taking into account scientific input by the EMA, to ensure that the concept of unmet medical need reflects scientific and technological developments and current knowledge in underserved diseases.

The period of regulatory data protection is followed by a period of market protection (two years), which remains unchanged under the proposed directive as compared to the existing rules.

With the additional conditional protection periods, the period of regulatory protection (data and market protection) can add up to 12 years for innovative medicines (if a new therapeutic indication is added after the initial marketing authorisation).

In addition, for a medicinal product addressing an unmet medical need, a company will benefit from an enhanced scientific and regulatory support scheme ('PRIME') and from accelerated assessment mechanisms. The PRIME support scheme will boost innovation in areas of unmet medical needs, allow pharmaceutical companies to speed up the development process and allow earlier patient access. The various elements of this criterion-based definition of unmet medical need (e.g "remaining

high morbidity or mortality") will be further specified in implementing acts, taking into account scientific input by the EMA, to ensure that the concept of unmet medical need reflects scientific and technological developments and current knowledge in underserved diseases.

Increased competition from earlier market entry of generic and biosimilar medicinal products

The 'Bolar exemption' (under which studies can be carried out for subsequent regulatory approval of generics and biosimilars during the patent or supplementary protection certificate protection of the reference medicinal product), will be broadened in scope and its harmonised application in all Member States ensured. In addition, procedures for the authorisation of generics and biosimilars will be simplified: as a general rule, risk management plans will no longer be required for generic and biosimilar medicinal products, considering that the reference medicinal product already has such a plan. The interchangeability of biosimilars with their reference medicinal products is also better recognised based on accumulated scientific experience with such medicinal products. In addition, the act provides an incentive for repurposing off-patent, added value medicinal products. This supports innovation, resulting in a new therapeutic indication that offers significant clinical benefit in comparison with existing therapies. Taken together, these measures will facilitate earlier market entry of generics and biosimilars, thus increasing competition and contributing to the objectives of promoting affordability of medicinal products and patient access.

Increased transparency on the contribution of public funding to research & development costs

Marketing authorisation holders will be required to publish a report listing all direct financial support received from any public authority or publicly funded body for the research and development of the medicinal product, whether successful or not successful. Such information will be easily accessible to the public on a dedicated webpage of the marketing authorisation holder and in the database of all medicinal products for human use authorised in the EU. Greater transparency around public funding for medicinal products development is expected to help maintain or improve access to affordable medicinal products.

Reducing the environmental impact of medicinal products

Strengthening the requirements for the environmental risk assessment (ERA) in the market authorisation of medicinal products will drive pharmaceutical companies to evaluate and limit potential adverse effects to the environment and public health. The scope of the ERA is extended to cover new protection goals such as the risks of antimicrobial resistance.

Reducing the regulatory burden and providing a flexible regulatory framework to support innovation and competitiveness

Reduction of the regulatory burden will be ensured by measures simplifying regulatory procedures and improving digitisation. These include provisions on electronic submission of applications and electronic product information (ePI) on authorised medicinal products, the latter being an option that Member States can opt for based on their particular readiness to replace the paper leaflet. Measures to reduce regulatory burden also include abolishing the renewal and the sunset clause. The reduction of administrative burden through simplification and digitisation measures

will benefit in particular to SMEs and not-for-profit entities involved in developing medicinal products. The various measures to reduce the regulatory burden will strengthen the competitiveness of the pharmaceutical sector.

Adapted frameworks with specific regulatory requirements tailored to the characteristics or methods inherent to certain, especially novel, medicinal products will ensure an agile and future-proof regulatory environment while keeping the existing high standards of quality, safety and efficacy. Such adapted frameworks could draw on the results of the regulatory sandboxes established in the proposed regulation.

The proposed directive provides rules for products which combine a medicinal product and a medical device and specifies the interplay with the medical devices legal framework. These provisions improve legal certainty in order to accommodate increasing innovation in this field. In addition, the interplay with the legislation on substances of human origin ('SoHO' as defined in the 'SoHO Regulation') is further clarified with a new definition of 'SoHO-derived medicinal product' and the possibility for the EMA to make a scientific recommendation on a medicinal product's regulatory status, under the classification mechanism proposed in the regulation, in consultation with the relevant SoHO regulatory body. The proposed directive also introduces measures to improve the application of hospital exemptions for advanced therapy medicinal products.

Specific provisions for new platform technologies[37] will facilitate the development and authorisation of such types of innovation for the benefit of patients.

Specific measures related to quality and manufacturing

The advent of new therapeutic approaches that have features such as very short shelf-lives, and which may be highly personalised, enable decentralised manufacture and use of patient-specific medicinal products. These paradigms of decentralised or personalised manufacturing require a shift away from existing regulatory frameworks that are designed to meet the regulatory expectations for large-scale centralised manufacture. The new legal framework incorporates a risk-based and flexible approach that will enable the manufacture or testing of a wide range of medicinal products in close proximity to the patient.

[37] When a certain process/method is used to manufacture specific individualised treatments, i.e. adjustments to the medicine are made based on the characteristics of the patient or the causing pathogen.

2023/0132 (COD)

Proposal for a

DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

on the Union code relating to medicinal products for human use, and repealing Directive 2001/83/EC and Directive 2009/35/EC

(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on the Functioning of the European Union, and in particular Articles 114(1) and 168(4)(c) thereof,

Having regard to the proposal from the European Commission,

After transmission of the draft legislative act to the national parliaments,

Having regard to the opinion of the European Economic and Social Committee,

Having regard to the opinion of the Committee of the Regions,

Acting in accordance with the ordinary legislative procedure,

Whereas:

(1) The Union general pharmaceutical legislation was established in 1965 with the dual objective of safeguarding public health and harmonising the internal market for medicines. It has developed considerably since then, but these overarching objectives have guided all revisions. The legislation governs the granting of marketing authorisations for all medicines for human use by defining conditions and procedures to enter and remain on the market. A fundamental principle is that a marketing authorisation is granted only to medicines with a positive benefit-risk balance after assessment of their quality, safety and efficacy.

(2) The most recent comprehensive revision took place between 2001 and 2004 while targeted revisions on post-authorisation monitoring (pharmacovigilance) and on falsified medicines were adopted subsequently. In the almost 20 years since the last comprehensive revision, the pharmaceutical sector has changed and has become more globalised, both in terms of development and manufacture. Moreover, science and technology have evolved at a rapid pace. However, there continues to be unmet medical needs, i.e. diseases without or only with suboptimal treatments. Moreover, some patients may not benefit from innovation because medicines may be unaffordable or not placed on the market in the Member State concerned. There is also a greater awareness of the environmental impact of medicines. More recently, the COVID-19 pandemic has stress tested the framework.

(3) This revision is part of the implementation of the Pharmaceutical strategy for Europe and aims to promote innovation, in particular for unmet medical needs, while reducing regulatory burden and the environmental impact of medicines; ensure access to innovative and established medicines for patients, with special attention to enhancing security of supply and addressing risks of shortages, taking into account the challenges

of the smaller markets of the Union; and create a balanced and competitive system that keeps medicines affordable for health systems while rewarding innovation.

(4) This revision focuses on provisions relevant to achieve its specific objectives; therefore it covers all but provisions concerning falsified medicines, homeopathic and traditional herbal medicines. Nevertheless, for the sake of clarity, it is necessary to replace Directive 2001/83/EC of the European Parliament and of the Council[1] with a new Directive. The provisions on falsified medicines, homeopathic medicines and traditional herbal medicines are therefore maintained in this Directive without changing their substance compared to previous harmonisations. However, in view of the changes in the governance of the Agency, the Herbal Committee is replaced by a working group.

(5) The essential aim of any rules governing the authorisation, manufacturing, supervision, distribution and use of medicinal products must be to safeguard public health. Such rules should also ensure the free movement of medicinal products and the elimination of obstacles to trade in medicinal products to all patients in the Union.

(6) The regulatory framework for medicinal products use should also take into account the needs of the undertakings in the pharmaceutical sector and trade in medicinal products within the Union, without jeopardising the quality, safety and efficacy of medicinal products.

(7) The EU and all its Member States as parties to the United Nations Convention on the Rights of Persons with Disabilities are bound by its provisions to the extent of their competences. This includes the right to access information as set out in Article 21 and the right to the enjoyment of the highest attainable standard of health without discrimination on the basis of disability as set in Article 25.

(8) This revision maintains the level of harmonisation that has been achieved. Where necessary and appropriate, it further reduces the remaining disparities, by laying down rules on the supervision and control of medicinal products and the rights and duties incumbent upon the competent authorities of the Member States with a view to ensuring compliance with legal requirements. In the light of experience gained on the application of the Union pharmaceutical legislation and the evaluation of its functioning, the regulatory framework need to be adapted to scientific and technological progress, the current market conditions and economic reality within the Union. Scientific and technological developments induce innovation and development of medicinal products, including for therapeutic areas where there is still unmet medical need. To harness these developments, the Union pharmaceutical framework should be adapted to meet scientific developments such as genomics, accommodate cutting edge medicinal products, e.g. personalised medicinal products and technological transformation such as data analytics, digital tools and the use of artificial intelligence. These adaptations also contribute to competitiveness of the Union pharmaceutical industry.

(9) Medicinal products for rare diseases and for children, should be subject to the same conditions as any other medicinal product concerning their quality, safety and efficacy, for example for what concerns the marketing authorisation procedures, quality and the pharmacovigilance requirements. However, specific requirements also

[1] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, p. 67).

apply to them considering their unique characteristics. Such requirements, which are currently defined in separate legislations, should be integrated in general pharmaceutical legal framework in order to ensure clarity and coherency of all the measures applicable to these medicinal products. Furthermore, as some medicinal products authorised for use in children are authorised by the Member States, specific provisions should be integrated in this Directive.

(10) The system of a directive and regulation for the general pharmaceutical legislation should be maintained to avoid fragmentation of national legislation on medicinal products for human use, given that the legislation is based on a system of national Member States and Union marketing authorisations. Member States national marketing authorisations are granted and managed on the basis of national law implementing the Union pharmaceutical law. The evaluation of the general pharmaceutical legislation has not shown that the choice of legal instrument has caused specific problems or created disharmonisation. In addition, a REFIT Platform[2] opinion in 2019 showed that there was not support among the Member States to turn Directive 2001/83/EC into a Regulation.

(11) The Directive should work in synergy with the Regulation to enable innovation and promote competitiveness of the Union pharmaceutical industry, in particular SMEs. In this respect a balanced system of incentives is proposed that rewards innovation especially in areas of unmet medical need and innovation that reaches patients and improves access across the Union. To make the regulatory system more efficient and innovation-friendly the Directive also aims at reducing administrative burden and simplifying procedures for undertakings.

(12) The definitions and scope of Directive 2001/83/EC should be clarified in order to achieve high standards for the quality, safety and efficacy of medicinal products and to address potential regulatory gaps, without changing the overall scope, due to scientific and technological developments, e.g. low-volume products, bedside-manufacturing or personalised medicinal products that do not involve an industrial manufacturing process.

(13) To avoid the duplication of requirements for medicinal products in this Directive and in the Regulation, the general standards in regards to quality, safety and efficacy of medicinal products laid down in this Directive shall be applicable to medicinal products covered by national marketing authorisation and also to medicinal products covered by centralised marketing authorisation. Therefore, the requirements for an application for medicinal product are valid for both, also the rules on prescription status, product information, regulatory protection and rules on manufacturing, supply, advertising, supervision and other national requirements shall be applicable to medicinal products covered by centralised marketing authorisation.

(14) The determination of whether a product falls within the definition of a medicinal product must be made on a case-by-case basis taking into account the factors set out in this Directive, such as the product's presentation or pharmacological, immunological or metabolic properties.

(15) In order to take account both of the emergence of new therapies and of the growing number of so-called 'borderline' products between the medicinal product sector and

[2] The EU's efforts to simplify legislation – 2019 Annual Burden survey, https://commission.europa.eu/system/files/2020-08/annual_burden_survey_2019_4_digital.pdf.

other sectors, certain definitions and derogations should be modified, so as to avoid any doubt as to the applicable legislation. With the same objective of clarifying situations when a product fully falls within the definition of a medicinal product and also meet the definition of other regulated products, the rules for medicinal products under this Directive apply. Furthermore, to ensure the clarity of applicable rules, it is also appropriate to improve the consistency of the terminology of the pharmaceutical legislation and clearly indicate the products excluded from the scope of this Directive.

(16) The new definition for a substance of human origin (SOHO) by the [SoHO Regulation] covers any substance collected from the human body in whatever manner, whether it contains cells or not and regardless of whether it meets the definition of 'blood', 'tissue' or 'cell', for example human breast milk, intestinal microbiota and any other SoHO that may be applied to humans in the future. Such substances of human origin, other than tissues and cells, may become SoHO derived medicinal products, other than ATMPs, when the SoHO is subject to an industrial process involving systematisation, reproducibility and operations performed on a routine basis or batch-wise resulting in a product of standardised consistency. When a process concerns extraction of an active ingredient from the SoHO, other than tissues and cells, or a transformation of a SoHO, other than tissues and cells, by changing its inherent properties, this should also be considered a SoHO derived medicinal product. When a process concerns concentrating, separating or isolating elements in the preparation of blood components, this should not be considered as changing their inherent properties.

(17) For avoidance of doubt, the safety and quality of human organs intended for transplantation are regulated only by Directive 2010/53/EU of the European Parliament and of the Council[3], and the safety and quality of substances of human origin intended for medically assisted reproduction are regulated only by [SoHO Regulation or if not in force, Directive 2004/23/EC].

(18) Advanced therapy medicinal products that are prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient, should be excluded from the scope of this Directive whilst at the same time ensuring that relevant Union rules related to quality and safety are not undermined ('hospital exemption'). Experience has shown that there are great differences in the application of hospital exemption among Member States. To improve the application of hospital exemption this Directive introduces measures for collection, reporting of data as well as review of these data yearly by the competent authorities and their publication by the Agency in a repository. Furthermore, the Agency should provide a report on the implementation of hospital exemption on the basis of contributions from Member States in order to examine whether an adapted framework should be established for certain less complex ATMPs that have been developed and used under the hospital exemption. When an authorisation for the manufacturing and use of an ATMP under hospital exemption is revoked because of safety concerns, the relevant competent authorities shall inform the competent authorities of other Member States.

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[3] Directive 2010/45/EU of the European Parliament and of the Council of 7 July 2010 on standards of quality and safety of human organs intended for transplantation (OJ L 207, 6.8.2010, p. 14).

(19) This Directive should be without prejudice to the provisions of Council Directive 2013/59/Euratom[4], including with respect to justification and optimisation of protection of patients and other individuals subject to medical exposure to ionising radiation. In the case of radiopharmaceuticals used for therapy, marketing authorisations, posology and administration rules have to notably respect that Directive's requirements that exposures of target volumes are to be individually planned, and their delivery appropriately verified taking into account that doses to non-target volumes and tissues are to be as low as reasonably achievable and consistent with the intended therapeutic purpose of the exposure.

(20) In the interest of public health, a medicinal product should only be allowed to be placed on the market in the Union when the marketing authorisation has been granted to the medicinal product, and its quality, safety and efficacy have been demonstrated. However, exemption should be provided from this requirement in situations characterised by an urgent need to administer a medicinal product to address the specific needs of a patient, or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation that could cause harm. In particular, to fulfil special needs, Member States should be allowed to exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised healthcare professional and for use by an individual patient under their direct personal responsibility. Member States should be also allowed to temporarily authorise the distribution of an unauthorised medicinal product in response to a suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation any of which could cause harm.

(21) Marketing authorisation decisions should be taken on the basis of the objective scientific criteria of quality, safety and efficacy of the medicinal product concerned, to the exclusion of economic or any other considerations. However, Member States should be able exceptionally to prohibit the use in their territory of medicinal products.

(22) The particulars and documentations that are to accompany an application for marketing authorisation for a medicinal product demonstrate that the therapeutic efficacy of the product overweight potential risks. The benefit-risk balance of all medicinal products will be assessed when they are placed on the market, and at any other time the competent authority deems appropriate.

(23) As market forces alone have proven insufficient to stimulate adequate research into, and the development and authorisation of, medicinal products for the paediatric population, a system of both obligations and rewards and incentives has been put in place.

(24) It is therefore necessary to introduce a requirement for new medicinal products or when developing paediatric indications of already authorised products covered by a patent or a supplementary protection certificate to present either the results of studies in the paediatric population in accordance with an agreed paediatric investigation plan or proof of having obtained a waiver or deferral, at the time of filing a marketing authorisation application or an application for a new therapeutic indication, new pharmaceutical form or new route of administration. However, in order to avoid

[4] Council Directive 2013/59/Euratom of 5 December 2013 laying down basic safety standards for protection against the dangers arising from exposure to ionising radiation, and repealing Directives 89/618/Euratom, 90/641/Euratom, 96/29/Euratom, 97/43/Euratom and 2003/122/Euratom (OJ L 13, 17.1.2014, p. 1).

exposing children to unnecessary clinical trials or due to the nature of the medicinal products, that requirement should not apply to generics or similar biological medicinal products and medicinal products authorised through the well-established medicinal use procedure, nor to homeopathic medicinal products and traditional herbal medicinal products authorised through the simplified registration procedures of this Directive.

(25) In order to ensure that the data supporting the marketing authorisation concerning the use of a product in children to be authorised under this regulation have been correctly developed, the competent authorities should check compliance with the agreed paediatric investigation plan and any waivers and deferrals at the validation step for marketing authorisation applications.

(26) In order to reward the compliance with all the measures included in the agreed paediatric investigation plan, for products covered by a supplementary protection certificate, if relevant information on the results of the studies conducted is included in the product information, a reward should be granted in the form of a six month extension of the supplementary protection certificate created by [Regulation (EC) No 469/2009 of the European Parliament and of the Council[5]- OP please replace reference by new instrument when adopted].

(27) Certain particulars and documentation that are normally to be submitted with an application for a marketing authorisation should not be required if a medicinal product is a generic medicinal product or a similar biological medicinal product (biosimilar) that is authorised or has been authorised in the Union. Both generic and biosimilar medicinal products are important to ensure access of medicinal products to a wider patient population and create a competitive internal market. In a joint statement authorities of the Member States confirmed that the experience with approved biosimilar medicinal products over the past 15 years has shown that in terms of efficacy, safety and immunogenicity they are comparable to their reference medicinal product and are therefore interchangeable and can be used instead of its reference product (or vice versa) or replaced by another biosimilar of the same reference product.

(28) Experience has shown that it is advisable to stipulate precisely the cases in which the results of toxicological and pharmacological tests or clinical studies do not have to be provided with a view to obtaining authorisation for a medicinal product that is essentially similar to an authorised product, while ensuring that innovative undertakings are not placed at a disadvantage. For these specified categories of medicinal products an abridged procedure allows applicants to rely on data submitted by previous applicants and therefore to submit only some specific documentation.

(29) For generic medicinal products only the equivalence of the generic medicinal product with the reference medicinal product has to be demonstrated. For biological medicinal products, only the results of comparability tests and studies are provided to the competent authorities. For hybrid medicinal products i.e. in cases where the medicinal product does not fall within the definition of a generic medicinal product or has changes in strength, pharmaceutical form, route of administration or therapeutic indications, compared to the reference medicinal product, the results of the appropriate non-clinical tests or clinical studies shall be provided to the extent necessary to

[5] Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the supplementary protection certificate for medicinal products (OJ L 152, 16.6.2009, p. 10).

establish a scientific bridge to the data relied upon in the marketing authorisation for the reference medicinal product. The same applies to bio-hybrids i.e. in cases where a biosimilar medicinal product has changes in strength, pharmaceutical form, route of administration or therapeutic indications, compared to the reference biological medicinal product. In the latter two situations, the scientific bridge establishes that the active substance of the hybrid does not differ significantly in properties with regard to safety or efficacy. Where it differs significantly in respect of those properties, the applicant needs to submit a full application.

(30) Regulatory decision-making on the development, authorisation and supervision of medicines may be supported by access and analysis of health data, including real world data i.e. health data generated outside of clinical studies, where appropriate. The competent authorities should be able to use such data, including via the European Health Data Space interoperable infrastructure.

(31) Directive 2010/63/EU of the European Parliament and of the Council[6] lays down provisions on the protection of animals used for scientific purposes based on the principles of replacement, reduction and refinement. Any study involving the use of animals, which provides essential information on the quality, safety and efficacy of a medicinal product, should take into account those principles of replacement, reduction and refinement, where they concern the care and use of live animals for scientific purposes, and should be optimised in order to provide the most satisfactory results whilst using the minimum number of animals. The procedures of such testing should be designed to avoid causing pain, suffering, distress or lasting harm to animals and should follow the available EMA and ICH guidelines. In particular, the marketing authorisation applicant and the marketing authorisation holder should take into account the principles laid down in Directive 2010/63/EU, including, where possible, use new approach methodologies in place of animal testing. These can include but are not limited to: in vitro models, such as microphysiological systems including organ-on-chips, (2D and 3D-) cell culture models, organoids and human stem cells-based models; in silico tools or read-across models.

(32) Procedures should be in place to facilitate joint animal testing, wherever possible, in order to avoid unnecessary duplication of testing using live animals covered by Directive 2010/63/EU. Marketing authorisation applicants and marketing authorisation holders should make all efforts to reuse animal study results and make the results obtained from animal studies publicly available. For abridged applications marketing authorisation applicants should refer to the relevant studies conducted for the reference medicinal product.

(33) With respect to clinical trials, in particular those conducted outside the Union, on medicinal products destined to be authorised within the Union, it should be verified, at the time of the evaluation of the marketing authorisation application, that these trials were conducted in accordance with the principles of good clinical practice and the ethical requirements equivalent to the provisions of Regulation (EU) 536/2014 of the European Parliament and of the Council[7].

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6 Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes (OJ L 276, 20.10.2010, p. 33).

7 Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (OJ L 158, 27.5.2014, p. 1).

(34) There is the possibility under certain circumstances for marketing authorisations to be granted, subject to specific obligations or conditions, on a conditional basis or under exceptional circumstances. The legislation should allow under similar circumstances for medicinal products with a standard marketing authorisation for new therapeutic indications to be authorised on a conditional basis or under exceptional circumstances. The products authorised on a conditional basis or under exceptional circumstances should in principle satisfy the requirements for a standard marketing authorisation with the exception of the specific derogations or conditions outlined in the relevant conditional or exceptional marketing authorisation and shall be subject to specific review of the fulfilment of the imposed specific conditions or obligations. The grounds for refusal of a marketing authorisation should apply *mutatis mutandis* for such cases.

(35) With the exception of those medicinal products that are subject to the centralised authorisation procedure established by [revised Regulation (EU) No. 726/2004], a marketing authorisation for a medicinal product should be granted by a competent authority in one Member State. In order to avoid unnecessary administrative and financial burdens for applicants and competent authorities, a full in-depth assessment of an application for the authorisation of a medicinal product should be carried out only once. It is appropriate therefore to lay down special procedures for the mutual recognition of national authorisations. Moreover, it should be possible to submit the same application in parallel in several Member States for the purpose of a common assessment under the lead of one of the Member States concerned.

(36) Moreover, rules should be established under those procedures to resolve any disagreements between competent authorities in a coordination group for mutual recognition and decentralised procedures medicinal products ('the coordination group') without undue delay. In the event of a disagreement between Member States about the quality, the safety or the efficacy of a medicinal product, a scientific evaluation of the matter should be undertaken according to a Union standard, leading to a single decision on the area of disagreement binding on the Member States concerned. Whereas this decision should be adopted by a rapid procedure ensuring close cooperation between the Commission and the Member States.

(37) In certain cases of major disagreement that cannot be solved, the case should be escalated and be subject to a scientific opinion of the Agency, which is then implemented through a Commission Decision.

(38) In order to better protect public health and avoid any unnecessary duplication of effort during the examination of application for a marketing authorisation for medicinal products, Member States should systematically prepare assessment reports in respect of each medicinal product that is authorised by them, and exchange the reports upon request. Furthermore, a Member State should be able to suspend the examination of an application for authorisation to place a medicinal product on the market that is currently under active consideration in another Member State with a view to recognising the decision reached by the latter Member State.

(39) In the interest of as broad as possible access to medicinal products, a Member State that has an interest in receiving access to a particular medicinal product undergoing authorisation through the decentralised and mutual recognition procedures should be able to opt-into that procedure.

(40) In order to increase availability of medicinal products, in particular on smaller markets, it should, in cases where an applicant does not apply for an authorisation for a medicinal product in the context of the mutual-recognition procedure in a given

Member State, be possible for that Member State, for justified public health reasons, to authorise the placing on the market of the medicinal product.

(41) In the case of generic medicinal products of which the reference medicinal product has been granted a marketing authorisation under the centralised procedure, applicants seeking marketing authorisation should be able to choose either of the two procedures, on certain conditions. Similarly, the mutual-recognition or decentralised procedure should remain available as an option for certain medicinal products, even if they represent a therapeutic innovation or are of benefit to society or to patients. Since generic medicines account for a major part of the market in medicinal products, their access to the Union market should be facilitated in the light of the experience acquired, therefore, the procedures to include other Member States concerned to such procedure should be further simplified.

(42) The simplification of procedures should not have an impact on standards or the quality of scientific evaluation of medicinal products to guarantee the quality, safety and efficacy and therefore, the scientific evaluation period should remain. However, the reduction of overall period for marketing authorisation procedure from 210 days to 180 days is foreseen.

(43) Member States should ensure adequate funding of competent authorities to carry out their tasks under this Directive and [revised Regulation (EU) 726/2004]. In addition, Member States should ensure adequate resources are assigned by the competent authorities for the purpose of their contributions to the work of the Agency, taking into account the cost-based remuneration they receive from the Agency.

(44) As regards access to medicinal products, previous amendments to the Union pharmaceutical legislation have addressed this issue by providing for accelerated assessment of marketing authorisation applications or by allowing conditional marketing authorisation for medicinal products for unmet medical need. While these measures accelerated the authorisation of innovative and promising therapies, these medicinal products do not always reach the patient and patients in the Union still have different levels of access to medicinal products. Patient access to medicinal products depends on many factors. Marketing authorisation holders are not obliged to market a medicinal product in all Member States; they may decide not to market their medicinal products in, or withdraw them from, one or more Member States. National pricing and reimbursement policies, the size of the population, the organisation of health systems and national administrative procedures are other factors influencing market launch and patient access.

(45) Addressing unequal patient access and affordability of medicinal products has become a key priority of the Pharmaceutical Strategy for Europe, as also highlighted by Council conclusions[8] and a resolution of the European Parliament[9]. Member States called for revised mechanisms and incentives for development of medicinal products tailored to the level of unmet medical need, while ensuring health system sustainability, patient access and availability of affordable medicinal products in all Member States.

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8 Council conclusions on strengthening the balance in the pharmaceutical systems in the EU and its Member States, (OJ C, C/269, 23.07.2016, p. 31). Council Conclusions on Access to medicines and medical devices for a Stronger and Resilient EU, (2021/C 269 I/02).

9 European Parliament resolution of 2 March 2017 on EU options for improving access to medicine (2016/2057(INI)) Shortages of medicines, 2020/2071(INI).

(46) Access also comprise affordability. In this regard, the Union pharmaceutical legislation respects the competence of the Member States in terms of pricing and reimbursement. In a complementary manner, it aims to have a positive impact on affordability and sustainability of health systems with measures that support competition from generic and biosimilar medicinal products. The competition from generic and biosimilar medicinal products should also, in turn, increase patient access to medicinal products.

(47) To ensure dialogue among all actors in the medicines lifecycle, discussions on policy issues related to the application of the rules related to prolongation of regulatory data protection for market launch shall take place in the Pharmaceutical Committee. The Commission may invite bodies responsible for health technology assessment as referred to in Regulation (EU) 2021/2282 or national bodies responsible for pricing and reimbursement, as required, to participate in the deliberations of the Pharmaceutical Committee.

(48) While pricing and reimbursement decisions are a Member State competence, the Pharmaceutical Strategy for Europe announced actions to support cooperation of Member States to improve affordability. The Commission has transformed the group of National Competent Authorities on Pricing and Reimbursement and public healthcare payers (NCAPR) from an ad-hoc forum to a continuous voluntary cooperation with the aim to exchange information and best practices on pricing, payment and procurement policies to improve the affordability and cost-effectiveness of medicines and health system's sustainability. The Commission is committed to stepping up this cooperation and further supporting information exchange among national authorities, including on public procurement of medicines, while fully respecting the competences of Member States in this area. The Commission may also invite NCAPR members to participate in deliberations of the Pharmaceutical Committee on topics that may have an impact on pricing or reimbursement policies, such as the market launch incentive.

(49) Joint procurement, whether within a country or across countries, can improve access, affordability, and security of supply of medicines, in particular for smaller countries. Member States interested in joint procurement of medicines can make use of Directive 2014/24/EU[10], which sets out purchasing procedures for public buyers, the Joint Procurement Agreement[11] and the proposed revised Financial Regulation[12]. Upon request from the Member States the Commission may support interested Member States by facilitating coordination to enable access to medicines for patients in the Union as well as information exchange, in particular for medicines for rare and chronic diseases.

(50) The establishment of a criteria-based definition of 'unmet medical need' is required to incentivise the development of medicinal products in therapeutic areas that are currently underserved. To ensure that the concept of unmet medical need reflects scientific and technological developments and current knowledge in underserved diseases, the Commission should specify and update using implementing acts, the criteria of satisfactory method of diagnosis, prevention or treatment, 'remaining high

[10] Directive 2014/24/EU of the European Parliament and of the Council of 26 February 2014 on public procurement and repealing Directive 2004/18/EC (OJ L 94, 28.3.2014, p. 65).

[11] Regulation (EU) 2022/2371 of the European Parliament and of the Council of 23 November 2022 on serious cross-border threats to health and repealing Decision No 1082/2013/EU.

[12] COM/2022/223 final.

morbidity or mortality', 'relevant patient population' following scientific assessment by the Agency. The Agency will seek input from a broad range of authorities or bodies active along the lifecycle of medicinal products in the framework of the consultation process established under the [revised Regulation (EC) No 726/2004] and also take into account scientific initiatives at EU level or between Member States related to analysing unmet medical needs, burden of disease and priority setting for research and development. The criteria for 'unmet medical need' can be subsequently used by Member States to identify specific therapeutic areas of interest.

(51) The inclusion of new therapeutic indications to an authorised medicinal products contributes to the access of patients to additional therapies and therefore should be incentivised.

(52) For the initial marketing authorisation application for medicinal products containing a new active substance, the submission of clinical trials that include as a comparator an evidence-based existing treatment should be incentivised, in order to foster the generation of comparative clinical evidence that is relevant and can accordingly support subsequent health technology assessments and decisions on pricing and reimbursement by Member States.

(53) A marketing authorisation holder should ensure the appropriate and continuous supply of a medicinal product throughout its lifetime irrespective of whether that medicinal product is covered by a supply incentive or not.

(54) Micro, small and medium-sized enterprises ('SMEs'), not-for-profit entities or entities with limited experience in the Union system should benefit from additional time to market a medicinal product in the Member States where the marketing authorisation is valid for the purposes of receiving additional regulatory data protection.

(55) When applying the provisions on market launch incentives, marketing authorisation holders and Member States should do their utmost to achieve a mutually agreed supply of medicinal products in accordance with the needs of the Member State concerned, without unduly delaying or hindering the other party from enjoying its rights under this Directive.

(56) Member States have the possibility to waive the condition of launch in their territory for the purpose of the prolongation of data protection for market launch. This can be done through a statement of non-objection to prolong the period of regulatory data protection. This is expected to be the case particularly in situations where launch in a particular Member State is materially impossible or because there are special reasons why a Member State wishes that launch take place later.

(57) The issuing of documentation from the Member States as regards the prolongation of data protection for the purpose of supply of medicinal products in all Member States where a marketing authorisation is valid, in particular the waiver to the conditions for such prolongation, does not affect at any time the powers of the Member States as regards the supply, setting of prices for medicinal products or their inclusion in the scope of national health insurance schemes. Member States do not waive the possibility to request release or supply of the product concerned at any time before, during or after the prolongation of the data protection period.

(58) An alternative way of demonstrating supply relates to the inclusion of medicinal products in a positive list of medicinal products covered by the national health insurance system in accordance with Directive 89/105/EEC. The related negotiations between companies and the Member State should be conducted in good faith.

(59) A Member State that considers that the conditions of supply have not been met for its territory should provide a reasoned statement of non-compliance at the latest in the Standing Committee on Medicinal Products for Human Use procedure of the variation linked to the provision of the relevant incentive.

(60) The Commission and Member States shall continuously monitor any data and learnings from the application of the incentives system in order to improve, including through implementing acts, how these provisions are applied. The Commission shall establish a list of national contact points in this regard.

(61) When a compulsory licence has been granted by a relevant authority in the Union to tackle a public health emergency, regulatory data protection may, if still in force, prevent the effective use of the compulsory licence as they impede the authorisation of generic medicinal products, and thus access to the medicinal products needed to address the crisis. For this reason, data and market protection should be suspended when a compulsory licence has been issued to tackle a public health emergency. Such a suspension of the regulatory data protection should be allowed only in relation to the compulsory licence granted and its beneficiary. The suspension shall comply with the objective, the territorial scope, the duration and the subject matter of the granted compulsory licence.

(62) The suspension of the regulatory data protection should be granted only for the duration of the compulsory licence. A ‘suspension‘ of data and market protection in cases of public health emergency shall mean that data and market protection shall produce no effect in relation to the particular licensee of the compulsory licence while that compulsory licence is in effect. When the compulsory licence ends, the data and market protection shall resume their effect. The suspension should not result in an extension of the original duration.

(63) It is currently possible for applicants for marketing authorisation of generic, biosimilar, hybrid and bio-hybrid medicinal products to conduct studies, trials and the subsequent practical requirements necessary to obtain regulatory approvals for those medicinal products during the term of protection of the patent or Supplementary Protection Certificate (SPC) of the reference medicinal product, without this being considered patent or SPC infringement. The application of this limited exemption is however fragmented across the Union and it is considered necessary, in order to facilitate the market entry of generic, biosimilar, hybrid and bio-hybrid medicinal products that rely on a reference medicinal product, to clarify its scope in order to ensure a harmonised application in all Member States, both in terms of beneficiaries and in terms of activities covered. The exemption must be confined to conduct studies and trials and other activities needed for the regulatory approval process, health technology assessment and pricing reimbursement request, even though this may require substantial amounts of test production to demonstrate reliable manufacturing. During the term of protection of the patent or SPC of the reference medicinal product, there can be no commercial use of the resulting final medicinal products obtained for the purposes of the regulatory approval process.

(64) It will allow, *inter alia*, to conduct studies to support pricing and reimbursement as well as the manufacture or purchase of patent protected active substances for the purpose of seeking marketing authorisations during that period, contributing to the market entry of generics and biosimilars on day one of loss of the patent or SPC protection.

(65) The competent authorities should refuse the validation for an application for a marketing authorisation referring to data of a reference medicinal product only on the basis of the grounds set out in this Directive. The same applies to any decision to grant, vary, suspend, restrict or revoke the marketing authorisation. The competent authorities cannot base their decision on any other grounds. In particular, those decisions cannot be based on the patent or SPC status of the reference medicinal product.

(66) In order to address the challenge of antimicrobial resistance, antimicrobials should be packaged in quantities that are appropriate for the therapy cycle relevant for that product and national rules on antimicrobial subject to prescription ensure that they are dispensed in a way that corresponds to the quantities described by the prescription.

(67) The provision of information to healthcare professionals and to patients on the appropriate use, storage and disposal of antimicrobials is a joint responsibility of marketing authorisation holders and of Member States who should ensure appropriate collection system for all medicinal products.

(68) While this Directive restricts the use of antimicrobials by setting certain categories of antimicrobials under prescription status, due to the growing antimicrobial resistance in the Union, competent authorities of the Member States should consider further measures for example expanding the prescription status of antimicrobials or the mandatory use of diagnostic tests before prescription. Competent authorities of the Member States should consider such further measures according to the level of antimicrobial resistance in their territory and the needs of patients.

(69) The pollution of waters and soils with pharmaceutical residues is an emerging environmental problem, and there is scientific evidence that the presence of those substances in the environment from their manufacturing, use and disposal poses a risk to the environment and public health. The evaluation of the legislation showed that strengthening of existing measures to reduce the impact of medicinal products' lifecycle on the environment and public health is required. Measures under this Regulation complement the main environmental legislation, in particular the Water Framework Directive (2000/60/EC[13]), the Environmental Quality Standard Directive (2008/105/EC[14]) the Groundwater Directive (2006/118/EC[15]), the Urban Wastewater Treatment Directive (91/271/EEC[16]), the Drinking Water Directive (2020/2184[17]) and the Industrial Emissions Directive (2010/75/EU[18]).

(70) Marketing authorisation applications for medicinal products in the Union should include an Environmental Risk Assessment (ERA) and risk mitigation measures. If the

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13 Directive 2000/60/EC of the European Parliament and of the Council of 23 October 2000 establishing a framework for Community action in the field of water policy (OJ L 327, 22.12.2000, p. 1).

14 Directive 2008/105/EC of the European Parliament and of the Council of 16 December 2008 on environmental quality standards in the field of water policy, amending and subsequently repealing Council Directives 82/176/EEC, 83/513/EEC, 84/156/EEC, 84/491/EEC, 86/280/EEC and amending Directive 2000/60/EC of the European Parliament and of the Council (OJ L 348, 24.12.2008, p. 84).

15 Directive 2006/118/EC of the European Parliament and of the Council of 12 December 2006 on the protection of groundwater against pollution and deterioration (OJ L 372, 27.12.2006, p. 19).

16 Council Directive 91/271/EEC of 21 May 1991 concerning urban waste-water treatment (OJ L 135, 30.5.1991, p. 40).

17 Directive (EU) 2020/2184 of the European Parliament and of the Council of 16 December 2020 on the quality of water intended for human consumption (recast) (OJ L 435, 23.12.2020, p. 1).

18 Directive 2010/75/EU of the European Parliament and of the Council of 24 November 2010 on industrial emissions (integrated pollution prevention and control) (recast) (OJ L 334, 17.12.2010, p. 17).

applicant fails to submit a complete or sufficiently substantiated environmental risk assessment or they do not propose risk mitigation measures to sufficiently address the risks identified in the environmental risk assessment, the marketing authorisation should be refused. The ERA should be updated when new data or knowledge about relevant risks become available.

(71) Marketing authorisation applicants should take into account environmental risk assessment procedures of other EU legal frameworks that may apply to chemicals dependent on their use. Further to this Regulation, there are four main other frameworks: (i) Industrial chemicals (REACH, (Regulation (EC) No 1907/2006); (ii) Biocides (Regulation (EC) No 528/2012); (iii) Pesticides (Regulation (EC) No 1107/2009); and (iv) Veterinary medicines (Regulation (EU) 2019/6)). As a part of the Green Deal, the Commission has proposed a 'one-substance one-assessment' (OS-OA) approach for chemicals[19], in order to increase the efficiency of the registration system, reduce costs and unnecessary animal testing.

(72) The emissions and discharges of antimicrobials to the environment from manufacturing sites may lead to antimicrobial resistance ("AMR"), which is a global concern regardless where the emissions and discharges take place. Therefore, the ERA scope should be extended to cover the risk of AMR selection during the entire life cycle of antimicrobials, including manufacturing.

(73) The proposal also includes provisions for a risk-based approach regarding the ERA obligations of marketing authorisation holders before October 2005 and the setting-up of an ERA monograph system for active substances. This ERA monograph system should be available to applicants for use when conducting an ERA for a new application.

(74) For medicinal products authorised prior to October 2005, without any ERA, specific provisions should be introduced to set up a risk based prioritisation programme for the ERA submission or update by the market authorisation holders.

(75) Cyprus, Ireland, Malta and Northern Ireland have historically relied on the supply of medicinal products from or through parts of the United Kingdom other than Northern Ireland. Following the withdrawal of the United Kingdom of Great Britain and Northern Ireland from the European Union and the European Atomic Energy Community, to prevent shortages of medicinal products and ultimately to ensure a high level of public health protection, specific derogations to this Directive need to be included for medicinal products supplied to Cyprus, Ireland, Malta and Northern Ireland from or through parts of the United Kingdom other than Northern Ireland. In order to ensure uniform application of Union law in the Member States, the derogations applicable in Cyprus, Ireland and Malta should be of a temporary nature only.

(76) To ensure that all children in the Union have access to the products specifically authorised for paediatric use, when an agreed paediatric investigation plan has led to the authorisation of a paediatric indication for a product already marketed for other therapeutic indications, the marketing authorisation holder should be obliged to place

[19] Communication from the Commission to the European Parliament, the European Council, the Council, the European Economic and Social Committee and the Committee of the Regions, The European Green Deal, Brussels (2019), COM(2019) 640 final.

the product in the same markets within two years of the date of approval of the indication.

(77) It is necessary in the interest of public health to ensure the continuing availability of safe and effective medicinal products authorised for paediatric indications. Therefore, if a marketing authorisation holder intends to withdraw such a medicinal product from the market then arrangements should be in place so that the paediatric population can continue to have access to the medicinal product in question. In order to help achieve this, the Agency should be informed in good time of any such intention and should make that intention publicly available.

(78) To avoid unnecessary administrative and financial burdens both for the marketing authorisation holders and the competent authorities, certain streamlining measures should be introduced, in line with the digital by default principle. Electronic application for marketing authorisation and for variations to the terms of the marketing authorisation should be introduced.

(79) As a general rule, risk management plans for generic and biosimilar medicinal products should not be developed and submitted, considering that the reference medicinal product has such a plan, except in specific cases, where a risk management plan should be provided. Furthermore, as a general rule a marketing authorisation should be granted for an unlimited period; exceptionally, one renewal may be decided only on justified grounds related to the safety of the medicinal product.

(80) In the event of a risk to public health, the marketing authorisation holder or the competent authorities should be able to make urgent safety or efficacy restrictions on their own initiative. In such case, when the referral procedure is launched, any duplication of assessment should be avoided.

(81) To address patients' needs, an increasing number of innovative medicinal products derive from or are combined with other products that may be manufactured or tested and regulated under more than one Union legal framework. Similarly, the same sites are increasingly overseen by the authorities established under different Union legal frameworks. To ensure safe and efficient production and supervision of such products and to allow an appropriate delivery to patients, it is important to ensure coherence. The coherence and sufficient alignment can only be ensured through appropriate cooperation in the development of the practices and principles applied under the different Union legal frameworks. An appropriate cooperation should therefore be embedded within several provisions of this Directive, such as those regarding classification advice, oversight, or the development of guidelines.

(82) For products that combine a medicinal product and a medical device the applicability of the two respective regulatory frameworks should be specified and the appropriate interaction between the two applicable regulatory frameworks should be ensured. The same should apply to combinations of medical products and products other than medical devices.

(83) To ensure that the competent authorities have all the information needed for their assessment in the case of integral combinations of a medicinal product with a medical device or of combinations of a medicinal product with a product other than a medical device, the marketing authorisation applicant shall submit data establishing the safe and effective use of the integral combination of the medicinal product with the medical device or of the combination of a medicinal product with the other product. The competent authority should assess the benefit-risk balance of the integral

combination taking into account the suitability of the use of the medicinal product together with the medical device or the other product.

(84) To ensure that the competent authorities have all the information needed for their assessment of medicinal products in exclusive use with a medical device (that is to say medicinal products that are presented in a package with a medical device or that are to be used with a medical device referenced in the summary of product characteristics) the marketing authorisation applicant shall submit data establishing the safe and effective use of the medicinal product taking into account its use with the medical device. The competent authority should assess the benefit-risk balance of the medicinal product, also taking into account the use of the medicinal product with the medical device.

(85) The Directive also clarifies that a medical device that is part of an integral combination has to comply with the general safety and performance requirements set out in Annex I of Regulation (EU) 2017/745 of the European Parliament and of the Council[20]. A medical device in exclusive use with a medical device needs to meet all of the requirements of Regulation (EU) 2017/745. A medicinal product in exclusive use with a medical device that is not ancillary to that of the medical device shall comply with the requirements of this Directive and of the [revised Regulation (EC) No 726/2004] taking into account its use with the medical device, without prejudice to the specific requirements of the Regulation (EU) 2017/745.

(86) For all these products (integral combinations of a medicinal product and a medical device, medicinal products in exclusive use with medical devices and combinations of a medicinal product with a product other than a medical device) the competent authority should also be able to request the marketing authorisation applicant to transmit any additional information needed and the marketing authorisation applicant should be bound to submit any such information requested. For medicinal product in exclusive use with a medical device that is not ancillary to that of the medical device, the marketing authorisation applicant shall also, upon request from the competent authority, submit any additional information related to the medical device taking into account its use with the medicinal product and that is relevant for the post-authorisation monitoring of the medicinal product, without prejudice to the specific requirements of the [revised Regulation (EC) No 726/2004].

(87) For integral combination of a medicinal product with a medical device and for combinations of a medicinal product with a product other than a medical device, the marketing authorisation holder should also bear the overall responsibility for the whole product in terms of compliance of the medicinal product with the requirements of this Directive and the [revised Regulation(EC) No 726/2004] and should ensure coordination of the information flow between the sectors throughout the assessment procedure and the lifecycle of the medicinal product.

(88) In order to ensure the quality, safety and efficacy of medicinal product at all stages of manufacturing and distribution the marketing authorisation holder shall be responsible, when necessary to trace back an active substance, excipient or any other substance that used in the manufacturing of medicinal product and intended to be part of the

[20] Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (OJ L 117, 5.5.2017, p. 1).

medicinal product or expected to be present in the medicinal product, for example impurities, degradation products or contaminants.

(89) In the interests of public health marketing authorisation holders should be able to ensure the traceability of any substance that is used, intended or expected to be present in a medicinal product at all stages of manufacturing and distribution, and identify any natural or legal person from whom they have been supplied these substances. Therefore, procedures and systems should be placed to provide that information in case it should be necessary with the view of quality, safety or efficacy of medicinal products.

(90) It is recognised that the development of pharmaceuticals is an area where neither science, nor technology stand still. The last decades have seen new categories of medicinal products emerging from biological medicinal products to biosimilars or advanced therapy medicinal products or in the future phages therapies. Those categories of products may in some instances require adapted rules to fully take account of their specific characteristics. For that reason a forward looking legal framework should include provisions to enable such adapted frameworks subject to strict criteria and under a Commission empowerment guided by the scientific input of the European Medicines Agency.

(91) The adaptations may entail adapted, enhanced, waived or deferred requirements compared to standard medicinal products. They could in particular include changes to the dossier requirements for such medicinal products, the way their quality, safety and efficacy is demonstrated by applicants or tailored manufacturing controls and good manufacturing practices requirements, as well as additional control methods prior and during their administration and use. The adaptions should however not go beyond what is necessary for the attainment of the objective of adaptation to the specific characteristics.

(92) In order to increase the preparedness and responsiveness against health threats, in particular the emergence of antimicrobial resistance, adapted frameworks may be relevant to facilitate the rapid change of antimicrobials composition to maintain their efficacy. The use of established platforms would allow efficient and timely adaptation of those medicinal products to the clinical context.

(93) To optimise the use of resources for both applicants for marketing authorisation and competent authorities and avoid duplication of assessment of chemical active substances of medicinal products, marketing authorisation applicants should be able to rely on an active substance master file certificate or a monograph of the European Pharmacopeia, instead of submitting the relevant data as required in accordance with Annex II. An active substance master file certificate may be granted by the Agency when the relevant data on the active substance concerned is not already covered by a monograph of the European Pharmacopeia or by another active substance master file certificate. The Commission should be empowered to establish the procedure for the single assessment of an active substance master file. To further optimise the use of resources, the Commission should be empowered to allow use a certification scheme also for additional quality master files i.e. for active substances other than chemical active substances, or for other substances present or used in the manufacture of a medicinal product, required in accordance with Annex II, e.g. in case of novel excipients, adjuvants, radiopharmaceutical precursors and active substance intermediates, when the intermediate is a chemical active substance by itself or used in conjugation with a biological substance.

(94) For reasons of public health and legal consistency, and with a view to reducing the administrative burden and strengthening predictability for economic operators, variations to all types of marketing authorisations should be subject to harmonised rules.

(95) The terms of a marketing authorisation for a medicinal product may be varied, after it has been granted. While the core elements of a variation are laid down in this Directive, the Commission should be empowered to complement these elements by laying down further necessary elements, to adapt the system to scientific and technological progress, including digitalisation, and to ensure that unnecessary administrative burden is avoided for both the marketing authorisation holders and competent authorities.

(96) Scientific and technological progresses in data analytics and data infrastructure provide valuable support to the development, authorisation and supervision of medicinal products. The digital transformation has affected regulatory decision-making, making it more data-driven and multiplying the possibilities for regulatory authorities to access evidence, across the lifecycle of a medicinal product. This Directive recognises the competent authorities of the Member States' capacity to access and analyse data submitted independently from the marketing authorisation applicant or marketing authorisation holder. On this basis, competent authorities of the Member States should take initiative to update the summary of product characteristics in case new efficacy or safety data impacts the benefit-risk balance of a medicinal product.

(97) Access to individual patient data from clinical studies in structured format allowing for statistical analyses is valuable to assist regulators in understanding the submitted evidence and to inform regulatory decision-making on the benefit-risk balance of a medicinal product. The introduction of such possibility in the legislation is important to further enable data-driven benefit-risk assessments at all stages of the lifecycle of a medicinal product. This Directive therefore empowers competent authorities of Member States to request such data as part of the assessment of initial and post-marketing authorisation applications. Due to the sensitive nature of health data, the competent authorities should safeguard its processing operations and ensure that they respect the data protection principles of lawfulness, fairness and transparency, purpose limitation, data minimisation, accuracy, storage limitation, integrity and confidentiality. Where the processing of personal data is necessary for the purposes of this Directive, such processing should be done in accordance with Union law on the protection of personal data. Any processing of personal data under this Directive should take place in accordance with Regulation (EU) 2016/679[21] and Regulation (EU) 2018/1725[22] of the European Parliament and of the Council.

(98) Pharmacovigilance rules are necessary for the protection of public health in order to prevent, detect and assess adverse reactions to medicinal products placed on the Union

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21 Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation) (OJ L 119, 4.5.2016, p. 1).

22 Regulation (EU) 2018/1725 of the European Parliament and of the Council of 23 October 2018 on the protection of natural persons with regard to the processing of personal data by the Union institutions, bodies, offices and agencies and on the free movement of such data, and repealing Regulation (EC) No 45/2001 and Decision No 1247/2002/EC (OJ L 295, 21.11.2018, p. 39).

market, as the full safety profile of medicinal products can only be known after they have been placed on the market.

(99) In order to ensure the continued safety of medicinal products in use, it is necessary to ensure that pharmacovigilance systems in the Union are continually adapted to take account of scientific and technical progress.

(100) It is necessary to take account of changes arising as a result of international harmonisation of definitions, terminology and technological developments in the field of pharmacovigilance.

(101) The increasing use of electronic networks for communication of information on adverse reactions to medicinal products marketed in the Union is intended to allow competent authorities to share the information at the same time.

(102) It is the interest of the Union to ensure that the pharmacovigilance systems for centrally authorised medicinal products and those authorised by other procedures are consistent.

(103) Marketing authorisation holders should be proactively responsible for on-going pharmacovigilance of the medicinal products they place on the market.

(104) The use of colours in human and veterinary medicinal products is currently regulated by Directive 2009/35/EC of the European Parliament and of the Council[23], and restricted to those authorised in accordance with Regulation (EC) No 1333/2008 of the European Parliament and of the Council on food additives[24], for which specifications are laid down in Commission Regulation (EU) No 231/2012[25]. Uses of excipients other than colours in medicinal products are subject to the Union rules on medicinal products and are evaluated as part of the overall benefit risk profile of a medicinal product.

(105) Experience has shown the need to maintain to a certain extent the principle of the use in medicinal products of those colours authorised as food additives. However, it is also appropriate to foresee a specific assessment for the use of the colour in medicines when a food additive is removed from Union list of food additives. Therefore, in this specific case, EMA should carry out its own assessment for the use of the colour in medicines, taking into account the EFSA opinion and its underlying scientific evidence, as well as any additional scientific evidence and giving particular consideration to the use in medicines. EMA should also be responsible for following any scientific evidence for the colours retained for specific medicine use only. Directive 2009/35/EC should therefore be repealed.

(106) With regard to the supervision and inspections, manufacturing and import of starting materials or intermediate and also of functional excipient shall be under surveillance due to their ancillary action to the active substance and to their possible impact to the quality, safety and efficacy to the medicinal products.

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23 Directive 2009/35/EC of the European Parliament and of the Council of 23 April 2009 on the colouring matters which may be added to medicinal products (OJ L 109, 30.4.2009, p. 10).

24 Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives (OJ L 354, 31.12.2008, p. 16).

25 Commission Regulation (EU) No 231/2012 of 9 March 2012 laying down specifications for food additives listed in Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council (OJ L 83, 22.3.2012, p. 1).

(107) The main purpose of any regulation on the manufacture and distribution of medicinal products should be to safeguard public health.

(108) It should be ensured that, in the Member States, the supervision and control of the manufacture and the distribution of medicinal products is carried out by official representatives of the competent authority who fulfils minimum conditions of qualification.

(109) There may be cases where manufacturing or testing steps of medicinal products need to take place in sites close to patients, for example advanced therapy medicinal products with short shelf-life. In such cases, these manufacturing or testing steps may need to be decentralised to multiple sites to reach patients across the Union. When the manufacturing or testing steps are decentralised, they should be carried out under the responsibility of the qualified person of an authorised central site. The decentralised sites should not require a separate manufacturing authorisation from the one granted to the relevant central site but should be registered by the competent authority of the Member State in which the decentralised site is established. In the case of medicinal products containing, consisting or derived from autologous SoHO, the decentralised sites have to be registered as a SoHO entity as defined in and pursuant to [SoHO Regulation] for the activities of donor review and eligibility assessment, donor testing and collection, or just for collection in the case of products manufactured for autologous use.

(110) The quality of medicinal products manufactured or available in the Union should be guaranteed by requiring that the active substances used in their composition comply with the principles of good manufacturing practice in relation to those medicinal products. It has proved necessary to reinforce the Union provisions on inspections and to compile a Union database of the results of those inspections.

(111) Verification of compliance with the legal requirements of manufacturing, distribution and use of medicinal products by relevant entities through a system of supervision, is of fundamental importance to ensure that the objectives of this Directive are effectively achieved. Therefore, the competent authorities of the Member States should have the power to perform on site or remote inspections, as part of the system of supervision at all stages of manufacturing, distribution and use of medicinal products or active substances and rely on the outcome of inspections conducted by trusted third countries competent authorities. To preserve the effectiveness of the inspections, the competent authorities should have the possibility to perform joint inspections and also, where necessary, unannounced inspections.

(112) The frequency of controls should be established by the competent authorities having regard to the risk and to the level of compliance expected in different situations. That approach should allow those competent authorities to allocate resources where the risk is the highest. In some cases, the system of supervision should be applied irrespective of the level of risk or suspected non-compliance, for example prior to granting manufacturing authorisations.

(113) Within the procedure for "Certification of Suitability to the monographs of the European Pharmacopoeia" the European Directorate for the Quality of Medicines and Healthcare verifies by means of inspections whether the data submitted by the applicant established by the Council of Europe confirms the suitability of monographs to control the chemical purity, microbiological quality and TSE risk (if relevant). It also verifies whether the manufacturing complies with good manufacturing practice for active substances. Depending of the outcome of the inspection, a certificate of

compliance or non-compliance of good manufacturing practice, is issued by the European Directorate for the Quality of Medicines and Healthcare or by the Member State participating in the inspection.

(114) Each undertaking that manufactures or imports medicinal products should set up a mechanism to ensure that all information supplied about a medicinal product conforms to the approved conditions of use.

(115) The conditions governing the supply of medicinal products to the public should be harmonised.

(116) In this connection persons moving around within the Union have the right to carry a reasonable quantity of medicinal products lawfully obtained for their personal use. It should also be possible for a person established in one Member State to receive from another Member State a reasonable quantity of medicinal products intended for their personal use.

(117) By virtue of [revised Regulation (EC) No 726/2004], certain medicinal products are the subject of a Union marketing authorisation. In this context, the prescription status of medicinal products covered by a Union marketing authorisation needs to be established. It is therefore important to set the criteria on the basis of which Union decisions will be taken.

(118) It is therefore appropriate to harmonise the basic principles applicable to the prescription status of medicinal products in the Union or in the Member State concerned, while taking as a starting point the principles already established on this subject by the Council of Europe as well as the work of harmonisation completed within the framework of the United Nations, concerning psychotropic or narcotic substances - the United Nations Single Convention of 1961 on narcotic drugs and Convention on Psychotropic Substances of 1971.

(119) Many operations involving the wholesale distribution of medicinal products may cover several Member States simultaneously.

(120) It is necessary to exercise control over the entire chain of distribution of medicinal products, from their manufacture or import into the Union through to supply to the public, so as to guarantee that such products are stored, transported and handled in suitable conditions. The requirements that should be adopted for this purpose will considerably facilitate the withdrawal of defective products from the market and allow more effective efforts against counterfeit products.

(121) Any person involved in the wholesale distribution of medicinal products should be in possession of a special authorisation. Pharmacists and persons authorised to supply medicinal products to the public, and who confine themselves to this activity, should be exempt from obtaining this authorisation. It is however necessary, in order to control the complete chain of distribution of medicinal products, that pharmacists and persons authorised to supply medicinal products to the public keep records showing transactions in products received.

(122) Marketing authorisation is to be subject to certain essential conditions and it is the responsibility of the Member State concerned to ensure that such conditions are met; whereas each Member State is to recognize authorisations granted by other Member States.

(123) Certain Member States impose on wholesalers who supply medicinal products to pharmacists and on persons authorised to supply medicinal products to the public

certain public service obligations. Those Member States should be able to continue to impose those obligations on wholesalers established within their territory. They should also be able to impose them on wholesalers in other Member States on condition that they do not impose any obligation more stringent than those that they impose on their own wholesalers and provided that such obligations may be regarded as warranted on grounds of public health protection and are proportionate in relation to the objective of such protection.

(124) Rules should be laid down as to how the labelling and package leaflets are to be presented.

(125) The provisions governing the information supplied to users should provide a high degree of consumer protection, in order that medicinal products may be used correctly on the basis of full and comprehensible information.

(126) The marketing of medicinal products whose labelling and package leaflets comply with this Directive should not be prohibited or impeded on grounds connected with the labelling or package leaflet.

(127) The use of electronic and technological possibilities other than paper package leaflets can facilitate access to medicinal products, medicinal products distribution and should always guarantee equal or better quality of information to all patients compared to the paper form of product information.

(128) Member States have varying levels of digital literacy and internet access. In addition, patient and healthcare professional needs may differ. It is therefore necessary that Member States have a discretion on the adoption of measures enabling the electronic provision of product information while ensuring that no patient is left behind, taking into account the needs of different age categories and the different levels of digital literacy in the population, and making sure that product information is easily accessible to all patients. Member States should progressively allow the possibility for electronic product information, while ensuring full compliance with the rules on protection of personal data, and adhere to harmonised standards developed at EU level.

(129) Where Member States decide that the package leaflet should be made available in principle only electronically, they should also ensure that a paper version of the package leaflet is to be made available on demand and without additonal cost to patients. They should also ensure that the information in digital format is easily accessible to all patients, for instance by including in the outer packaging of the product a digitally readable barcode, which would direct the patient to the electronic version of the package leaflet.

(130) The use of multi-language packages can be a tool for access to medicinal products, in particular for small markets and in public health emergencies. Where multi-language packages are used, Member States may allow the use on the labelling and package leaflet of an official language of the Union that is commonly understood in the Member States where the multi-language package is marketed.

(131) To ensure a high level of transparency of public support to the research and development of medicinal products, the reporting of public contribution for the development of a particular medicinal product should be a requirement for all medicines. Given however the practical difficulty to identify how indirect public funding instruments, such as tax advantages, have supported a particular product, the reporting obligation should only concern the direct public financial support, such as

direct grants or contracts. Therefore, the provisions of this Directive ensure, without prejudice to the rules on the protection of confidential and personal data, transparency regarding any direct financial support received from any public authority or public body to carry out any activities for the research and development of medicinal products.

(132) To ensure the accuracy of the information made publicly available by the marketing authorisation holder, the declared information has to be subject to audit by an independent auditor.

(133) In order to ensure a harmonised and consistent reporting of public contribution for the development of a particular medicinal products, the Commission should be able to adopt implementing acts to clarify the principles and format that the marketing authorisation holder should adhere to when reporting this information.

(134) This Directive is without prejudice to the application of measures adopted pursuant to Directive 2006/114/EC of the European Parliament and of the Council[26] or pursuant to Directive 2005/29/EC of the European Parliament and of the Council[27]. Therefore the provisions regarding the advertising of medicinal products of this Directive should therefore be considered, where relevant, as a *lex specialis* with respect to Directive 2005/29/EC.

(135) Advertising, even of medicinal products not subject to a prescription, could affect public health and distort competition. Therefore, advertising of medicinal products should meet certain criteria. Persons qualified to prescribe, administer or supply medicinal products can properly evaluate the information available in advertising because of their knowledge, training and experience. The advertising of medicinal products to persons who cannot properly assess the risk associated with their use may lead to medicinal product misuse or overconsumption which is liable to harm public health. Therefore advertisement to the general public of medicinal products that are available only on medical prescription should be prohibited. Furthermore, distribution of samples free of charge to the general public for promotional ends is to be prohibited, also teleshopping for medicinal products shall be prohibited pursuant to Directive 2010/13/EU of the European Parliament and of the Council[28]. It should be possible within certain restrictive conditions to provide samples of medicinal products free of charge to persons qualified to prescribe or supply them so that they can familiarise themselves with new products and acquire experience in dealing with them.

(136) Advertising of medicinal products should aim at disseminating objective and unbiased information about the medicinal product. For that purpose, it is expressly forbidden highlight negatively another medicinal product or to suggest that advertised medicinal product might be safer or more effective than another medicinal product. Comparison

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[26] Directive 2006/114/EC of the European Parliament and of the Council of 12 December 2006 concerning misleading and comparative advertising (OJ L 376, 27.12.2006, p. 21).

[27] Directive 2005/29/EC of the European Parliament and of the Council of 11 May 2005 concerning unfair business-to-consumer commercial practices in the internal market and amending Council Directive 84/450/EEC, Directives 97/7/EC, 98/27/EC and 2002/65/EC of the European Parliament and of the Council and Regulation (EC) No 2006/2004 of the European Parliament and of the Council ('Unfair Commercial Practices Directive') (OJ L 149, 11.6.2005, p. 22).

[28] Directive 2010/13/EU of the European Parliament and of the Council of 10 March 2010 on the coordination of certain provisions laid down by law, regulation or administrative action in Member States concerning the provision of audiovisual media services (Audiovisual Media Services Directive) (OJ L 095 15.4.2010, p. 1).

of medicinal products should only be allowed if such information is listed in the summary of product characteristics of the medicinal product being advertised. This prohibition covers any medicinal product, also biosimilars, and therefore it would be misleading to refer in the advertising, that a biosimilar medicinal product would not be interchangeable with the original biological medicinal product or another biosimilar from the same original biological medicinal product. Additional strict rules about negative and comparative advertising of competitor medicinal products will prohibit claims that can mislead persons qualified to prescribe, administer or supply them.

(137) The dissemination of information which encourages the purchase of medicinal products should be considered within the concept of advertising of medicinal products, even where that information does not refer to a specific medicinal product, but to unspecified medicinal products.

(138) Advertising of medicinal products should be subject to strict conditions and effective, adequate monitoring. Reference in this regard should be made to the monitoring mechanisms set up by Directive 2006/114/EC.

(139) Medical sales representatives have an important role in the promotion of medicinal products. Therefore, certain obligations should be imposed upon them, in particular the obligation to supply the person visited with a summary of product characteristics.

(140) Innovative, 'combination medicinal products' and other developed medicinal products are complex in regards to their composition and administration. Therefore, in addition to persons qualified to prescribe medicinal products, also persons qualified to administer medicinal products need to be familiar with all characteristics of those medicinal products, especially with safe administration and use, including the comprehensive instructions to the patients. For that purpose information about medicinal products subject to medical prescription is also clearly allowed to persons qualified to administer them.

(141) Persons qualified to prescribe, administer or supply medicinal products should have access to a neutral, objective source of information about products available on the market. Whereas it is nevertheless for the Member States to take all measures necessary to this end, in the light of their own particular situation.

(142) In order to ensure that information on the use of the medicinal products in children are appropriately taken into account at the moment of marketing authorisation, it is therefore necessary to introduce a requirement for new medicinal products or when developing paediatric indications of already authorised products covered by a patent or a supplementary protection certificate, to present either the results of studies in the paediatric population in accordance with an agreed paediatric investigation plan or proof of having obtained a waiver or deferral, at the time of filing a marketing authorisation application or an application for a new therapeutic indication, new pharmaceutical form or new route of administration. In order to ensure that the data supporting the marketing authorisation concerning the use of a product in children, the competent authorities responsible for the authorisation of a medicinal product should check compliance with the agreed paediatric investigation plan and any waivers and deferrals at the validation step for marketing authorisation applications.

(143) To provide healthcare professionals and patients with information on the safe and effective use of medicinal products in the paediatric population, the results of the studies conducted in accordance with a paediatric investigation plan, independently from the fact that they support or not the use of the medicinal product in children,

appropriate information should be included in the summary of product characteristics and, if appropriate, in the package leaflet. Information on waivers should also be included in product information. When all the measures in the paediatric investigation plan have been complied with, that fact should be recorded in the marketing authorisation, and that should then be the basis upon which companies can obtain rewards.

(144) Relevant data and information collected through clinical studies conducted before the introduction in the Union of a paediatric medicines Regulation and received by the competent authorities should be assessed without undue delay and taken into consideration for eventual variation of existing marketing authorisations.

(145) In order to ensure uniform conditions for the implementation of this Regulation, implementing powers should be conferred on the Commission. Those powers should be exercised in accordance with Regulation (EU) No 182/2011 of the European Parliament and of the Council[29].

(146) Due to the need to reduce overall approval times for medicinal products, the time between the opinion of the Committee for Medicinal Products for Human Use (CHMP) and the final decision on any Commission Decision concerning national marketing authoristions, in particular for referrals, should be reduced to, in principle, 46 days.

(147) On the basis of the opinion of the Agency, the Commission should adopt a decision on the referral by means of implementing acts. In justified cases, the Commission may return the opinion for further examination or deviate in its decision from the opinion of the Agency. Taking into account the need to make medicinal products swiftly available to patients, it should be acknowledged that the chairperson of the Standing Committee for Medicines for Human Use will use the available mechanisms under Regulation 182/2011 and notably the possibility to obtain the committees opinion in written procedure and within expeditious deadlines which, in principle, will not exceed 10 calendar days.

(148) The Commission should be empowered to adopt any necessary changes to Annex II in order to take into account scientific and technical progress.

(149) In order to supplement or amend certain non-essential elements of this Directive, the power to adopt acts in accordance with Article 290 TFEU should be delegated to the Commission in respect of specifying the procedure for examination of application of active substance master file certificate, the publication of such certificates, the procedure for changes to the active substance master file and its certificate, access to the active substance master file and its assessment report; specifying additional quality master files to provide information on a constituent of a medicinal product, the procedure for examination of application of a quality master file certificate, the publication of such certificates, the procedure for changes to the quality master file and its certificate, and access to the quality master file and its assessment report; determining the situations in which post-authorisation efficacy studies may be required; specifying the categories of medicinal products to which a marketing authorisation subject to specific obligations could be granted and specifying the

[29] Regulation (EU) No 182/2011 of the European Parliament and of the Council of 16 February 2011 laying down the rules and general principles concerning mechanisms for control by Member States of the Commission's exercise of implementing powers (OJ L 55, 28.2.2011, p. 13).

procedures and requirements for granting such a marketing authorisation and for its renewal; specifying exemptions to variation and the categories in which variations should be classified and establishing procedures for the examination of applications for variations to the terms of marketing authorisations as well as specifying conditions and procedures for cooperation with third countries and international organisations for examination of applications for such variations. It is of particular importance that the Commission carry out appropriate consultations during its preparatory work, including at expert level, and that those consultations be conducted in accordance with the principles laid down in the Interinstitutional Agreement of 13 April 2016 on Better Law-Making[30]. In particular, to ensure equal participation in the preparation of delegated acts, the European Parliament and the Council receive all documents at the same time as Member States' experts, and their experts systematically have access to meetings of Commission expert groups dealing with the preparation of delegated acts.

(150) This Directive seeks to enable the right access to preventive healthcare and to benefit from medical treatment under the conditions established by national laws and practices and to ensure a high level of human health protection in the definition and implementation of all the Union's policies and activities as laid down in Article 35 of the Charter of Fundamental Rights of the European Union.

(151) Since the objectives of this Directive, namely to establish rules on medicinal products ensuring the protection of public health and the environment as well as the functioning of the internal market, cannot be sufficiently achieved by the Member States as national rules would lead to disharmonisation, unequal patient access to medicinal products and barriers to the internal market, but can rather, by reason of its effects, be better achieved at Union level, the Union may adopt measures, in accordance with the principle of subsidiarity as set out in Article 5 of the Treaty on European Union. In accordance with the principle of proportionality, as set out in that Article, this Directive does not go beyond what is necessary in order to achieve those objectives.

(152) In accordance with the Joint Political Declaration of 28 September 2011 of Member States and the Commission on explanatory documents[31], Member States have undertaken to accompany, in justified cases, the notification of their transposition measures with one or more documents explaining the relationship between the components of a directive and the corresponding parts of national transposition instruments. With regard to this Directive, the legislator considers the transmission of such documents to be justified.

HAVE ADOPTED THIS DIRECTIVE:

Chapter I:
Subject matter, scope and definitions

Article 1

Subject matter and scope

1. This Directive lays down rules for the placing on the market, manufacturing, import, export, supply, distribution, pharmacovigilance, control and use of medicinal products for human use.

30 OJ L 123, 12.5.2016, p. 1.
31 OJ C 369, 17.12.2011, p. 14.

2. This Directive shall apply to medicinal products for human use intended to be placed on the market.

3. In addition to the products referred to in paragraph 2, Chapter XI shall also apply to starting materials, active substances, excipients and intermediate products.

4. In cases where, taking into account all its characteristics, a product falls within the definition of a 'medicinal product' and within the definition of a product covered by other Union law and there is a conflict between this Directive and other Union law, the provisions of this Directive shall prevail.

5. The Directive shall not apply to:

   (a) medicinal products prepared in a pharmacy in accordance with a medical prescription for an individual patient ('magistral formula');

   (b) medicinal product prepared in a pharmacy in accordance with a pharmacopoeia and intended to be supplied directly to the patients served by the pharmacy in question ('officinal formula');

   (c) investigational medicinal product as defined in Article 2, paragraph 5, of Regulation (EU) No 536/2014.

6. Medicinal products referred to in paragraph 5, point (a), may be prepared in duly justified cases in advance by a pharmacy serving a hospital, on the basis of the estimated medical prescriptions within that hospital for the following seven days.

7. Member States shall take the necessary measures to develop the production and use of medicinal products derived from substances of human origin coming from voluntary unpaid donations.

8. This Directive and all Regulations referred to therein shall be without prejudice to the application of national legislation prohibiting or restricting the use of any specific type of substance of human origin or animal cells, or the sale, supply or use of medicinal products containing, consisting of or derived from these animal cells or substances of human origin, on grounds not dealt with in the aforementioned Union law. The Member States shall communicate the national legislation concerned to the Commission.

9. The provisions of this Directive shall not affect the powers of the Member States' authorities either as regards the setting of prices for medicinal products or their inclusion in the scope of national health insurance schemes, on the basis of health, economic and social conditions.

10. This Directive shall not affect the application of national legislation prohibiting or restricting the following:

   (a) the sale, supply or use of medicinal products as contraceptives or abortifacients;

   (b) the use of any specific type of substance of human origin or animal cells, on grounds not dealt with in the aforementioned Union law;

   (c) the sale, supply or use of medicinal products containing, consisting of or derived from these animal cells or substances of human origin, on grounds not dealt with in Union law.

Article 2

Advanced therapy medicinal products prepared under hospital exemption

1. By way of derogation from Article 1(1), only this Article shall apply to advanced therapy medicinal products prepared on a non-routine basis in accordance with the requirements set in paragraph 3 and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient ('advanced therapy medicinal products prepared under hospital exemption').

2. The manufacturing of an advanced therapy medicinal product prepared under hospital exemption shall require an approval by the competent authority of the Member State ('hospital exemption approval'). Member States shall notify any such approval, as well as subsequent changes, to the Agency.

   The application for a hospital exemption approval shall be submitted to the competent authority of the Member State where the hospital is located.

3. Member States shall ensure that advanced therapy medicinal products prepared under hospital exemption comply with the requirements equivalent to the good manufacturing practices and traceability for advanced therapy medicinal products referred to in Articles 5 and 15 of Regulation (EC) No 1394/2007 [32] respectively, and with pharmacovigilance requirements equivalent to those provided for at Union level pursuant to [revised Regulation (EC) No 726/2004].

4. Member States shall ensure that data on the use, safety and the efficacy of advanced therapy medicinal products prepared under hospital exemption is collected and reported by the hospital exemption approval holder to the competent authority of the Member State at least annually. The competent authority of the Member State shall review such data and shall verify the compliance of advanced therapy medicinal products prepared under hospital exemption with the requirements referred to in paragraph 3.

5. If a hospital exemption approval is revoked due to safety or efficacy concerns the competent authority of the Member States that approved the hospital exemption shall inform the Agency and the competent authorities of the other Member States.

6. The competent authority of the Member State shall transmit the data related to the use, safety and efficacy of an advanced therapy medicinal product prepared under the hospital exemption approval to the Agency annually. The Agency shall, in collaboration with the competent authorities of Member States and the Commission, set up and maintain a repository of that data.

7. The Commission shall adopt implementing acts to specify the following:

   (a) details of the application for the approval of hospital exemption referred to in paragraph 1, second subparagraph, including the evidence on quality, safety and efficacy of the advance therapy medicinal products prepared under hospital exemption for the approval and the subsequent changes;

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[32] Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (OJ L 324, 10.12.2007, p. 1).

(b) the format for collection and reporting of data referred to in paragraph 4;

(c) the modalities for the exchange of knowledge between hospital exemption approval holders within the same Member State or different Member States;

(d) the modalities for preparation and use of advanced therapy medicinal products under hospital exemption on a non-routine basis.

Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 214(2).

8. The Agency shall provide to the Commission a report on the experience acquired with the hospital exemption approvals on the basis of contributions from Member States and the data referred to in paragraph 4. The first report shall be provided three years after [OP please insert the date =18 months after the date of entering into force of this Directive] and then every five years thereafter.

Article 3

Exceptions under certain circumstances

1. A Member State may, in order to fulfil special needs, exclude from the scope of this Directive medicinal products supplied in response to a bona fide unsolicited order, prepared in accordance with the specifications of an authorised healthcare professional and for use by an individual patient under their direct personal responsibility. However, in such case Member States shall encourage healthcare professionals and patients to report data on the safety of the use of such products to the competent authority of the Member State in accordance with Article 97.

   For allergen medicinal products supplied in accordance with this paragraph, the competent authorities of the Member State may request the submission of relevant information in accordance with Annex II.

2. Without prejudice to Article 30 of [revised Regulation (EC) No 726/2004], Member States may temporarily authorise the use and distribution of an unauthorised medicinal product in response to a suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation any of which could cause harm.

3. Member States shall ensure that marketing authorisation holders, manufacturers and healthcare professionals are not subject to civil or administrative liability for any consequences resulting from the use of a medicinal product otherwise than for the authorised therapeutic indications or from the use of an unauthorised medicinal product, where such use is recommended or required by a competent authority in response to the suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation any of which could cause harm. Such provisions shall apply whether or not a national or a centralised marketing authorisation has been granted.

4. Liability for defective products, as provided for by [Council Directive 85/374/EEC[33] – OP please replace reference by new instrument COM(2022) 495 when adopted], shall not be affected by paragraph 3.

[33] Council Directive 85/374/EEC of 25 July 1985 on the approximation of the laws, regulations and administrative provisions of the Member States, concerning liability for defective products (OJ L 210, 7.8.1985, p. 29).

Article 4

Definitions

1. For the purposes of this Directive, the following definitions apply:

(1) ‘medicinal product’ means any substance or combination of substances that fulfils at least one of the following conditions:

(a) any substance or combination of substances that is presented as having properties for treating or preventing disease in human beings; or

(b) any substance or combination of substances that may be used in or administered to human beings with a view to either restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis;

(2) ‘substance’ means any matter irrespective of origin, which may be:

(a) human, e.g. tissues and cells, human blood, human secretions and human blood products;

(b) animal, e.g. whole animals, animal organs and parts thereof, animal tissues and cells, animal secretions, toxins, extracts, animal blood and animal blood products;

(c) vegetal, e.g. plants, including algae, parts of plants, plant secretions and exudates, extracts;

(d) chemical, e.g. elements, naturally occurring chemical materials and chemical products obtained by chemical change or synthesis;

(e) micro-organisms, e.g. bacteria, viruses and protozoa;

(f) fungi, including micro-fungi (yeast);

(3) ‘active substance’ means any substance or mixture of substances intended to be used in the manufacture of a medicinal product and that, when used in its production, becomes an active ingredient of that product intended to exert a pharmacological, immunological or metabolic action with a view to restoring, correcting or modifying physiological functions or to make a medical diagnosis;

(4) ‘starting material’ means any material from which an active substance is manufactured or extracted;

(5) ‘excipient’ means any ingredient of a medicinal product other than the active substance;

(6) ‘functional excipient’ means an excipient that contributes to or enhances the performance of a medicinal product or performs an action ancillary to that of the active substance but does not have a therapeutic contribution on its own;

(7) ‘advanced therapy medicinal product’ means advanced therapy medicinal product as defined in Article 2(1), point (a), of Regulation (EC) No 1394/2007;

(8) ‘allergen product’ means any medicinal product that is intended to identify or induce a specific acquired alteration in the immunological response to an allergen;

(9) ‘competent authorities’ means the Agency and the competent authorities of the Members States;

(10) ‘Agency’ means the European Medicines Agency;

(11) ‘non-clinical’ means a study or a test conducted in vitro, in silico, or in chemico, or a non-human in vivo test related to the investigation of the safety and efficacy of a medicinal product. Such test may include simple and complex human cell-based assays, microphysiological systems including organ-on-chip, computer modelling, other non-human or human biology-based test methods, and animal-based tests;

(12) ‘reference medicinal product’ means a medicinal product that is or has been authorised in the Union under Article 5, in accordance with Article 6;

(13) ‘generic medicinal product’ means a medicinal product that has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product;

(14) ‘biological medicinal product’ means a medicinal product, the active substance of which is produced by or extracted from a biological source and which due to its complexity, its characterisation and the determination of its quality may require a combination of physico-chemical-biological testing, together with its control strategy;

(15) ‘letter of access’ means an original document, signed by the owner of the data or its representative, that states that the data may be used for the benefit of a third party by a competent authority or the Commission for the purposes of this Directive;

(16) ‘fixed dose combination medicinal product’ means a medicinal product consisting of a combination of active substances intended to be placed on the market as a single pharmaceutical form;

(17) ‘multi-medicinal product package’ means a package that contains more than one medicinal product under a single invented name and intended to be used in a medical treatment where the individual medicinal products in the package are for medical purposes simultaneously or sequentially administered;

(18) ‘radiopharmaceutical’ means any medicinal product that, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a medicinal purpose;

(19) ‘radionuclide generator’ means any system incorporating a fixed parent radionuclide from which is produced a daughter radionuclide which is to be obtained by elution or by any other method and used in a radiopharmaceutical;

(20) ‘kit’ means any preparation to be reconstituted or combined with radionuclides in the final radiopharmaceutical, usually prior to its administration;

(21) ‘radionuclide precursor’ means any other radionuclide produced for the radio-labelling of another substance prior to administration;

(22) ‘antimicrobial’ means any medicinal product with a direct action on micro-organisms used for treatment or prevention of infections or infectious diseases, including antibiotics, antivirals and antifungals;

(23) ‘integral combination of a medicinal product with a medical device’ means a combination of a medicinal product with a medical device, as defined by Regulation (EU) 2017/745, and where:

(a) the two form an integral product and where the action of the medicinal product is principal and not ancillary to that of the medical device, or

(b) the medicinal product is intended to be administered by the medical device and the two are placed on the market in such a way that they form a single integral product that is intended exclusively for use in the given combination and where the medical device is not reusable.

(24) ‘combined advanced therapy medicinal products’ means a product as defined in Article 2 of Regulation (EC) No 1394/2007, including when a gene therapy medicinal product is part of the combined advanced therapy medicinal product;

(25) ‘medicinal product in exclusive use with a medical device’ means a medicinal product presented in a package with a medical device or to be used with a specific medical device, as defined by Regulation (EU) 2017/745, and referenced in the summary of product characteristics;

(26) ‘combination of a medicinal product with a product other than a medical device’ means a combination of a medicinal product with a product other than a medical device (as defined by Regulation (EU) 2017/745) and where the two are intended for use in the given combination in accordance with the summary of product characteristics;

(27) ‘immunological medicinal product’ means:

(a) any vaccine or allergen product, or

(b) any medicinal product consisting of toxins or serums used to produce passive immunity or to diagnose the state of immunity;

(28) 'vaccine’ means any medicinal product that is intended to elicit an immune response for prevention, including post exposure prophylaxis, and for treatment of diseases caused by an infectious agent;

(29) ‘gene therapy medicinal product’ means a medicinal product, except vaccines against infectious diseases, that contains or consists of:

(a) a substance or a combination of substances intended to edit the host genome in a sequence-specific manner or that contain or consists of cells subjected to such modification; or

(b) a recombinant or synthetic nucleic acid used in or administered to human beings with a view to regulating, replacing or adding a genetic sequence that mediates its effect by transcription or translation of the transferred genetic materials or that contain or consists of cells subjected to these modifications;

(30) ‘somatic cell therapy medicinal product’ means a biological medicinal product that has the following characteristics:

(a) contains or consists of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use

have been altered, or of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor;

(b) is presented as having properties for, or is used in or administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.

For the purposes of point (a), the manipulations listed in Annex I to Regulation (EC) No 1394/2007, in particular, shall not be considered as substantial manipulations.

(31) 'SoHO-derived medicinal product other than ATMPs' means any medicinal product containing, consisting of or deriving from a substance of human origin (SoHO), as defined in Regulation [SoHO Regulation], other than tissues and cells, that is of standardised consistency and is prepared by:

(a) a method involving an industrial process which includes pooling of donations; or

(b) a process that extracts an active ingredient from the substance of human origin or transforms the substance of human origin by changing its inherent properties;

(32) 'risk management plan' means a detailed description of the risk management system;

(33) 'environmental risk assessment' means the evaluation of the risks to the environment, or risks to public health, posed by the release of the medicinal product in the environment from the use and disposal of the medicinal product and the identification of risk prevention, limitation and mitigation measures. For medicinal product with an antimicrobial mode of action, the ERA also encompasses an evaluation of the risk for antimicrobial resistance selection in the environment due to the manufacturing, use and disposal of that medicinal product;

(34) 'antimicrobial resistance' means the ability of a micro-organism to survive or to grow in the presence of a concentration of an antimicrobial agent that is usually sufficient to inhibit or kill that micro-organism;

(35) 'risks related to use of the medicinal product' means any risk:

(a) relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health;

(b) of undesirable effects on the environment posed by the medicinal product;

(c) of undesirable effects on public health due to the release of the medicinal product in the environment including anti-microbial resistance;

(36) 'active substance master file' means a document that contains a detailed description of the manufacturing process, quality control during manufacture and process validation prepared in a separate document by the manufacturer of the active substance;

(37) 'paediatric investigation plan' means a research and development programme aimed at ensuring that the necessary data are generated determining the

conditions in which a medicinal product may be authorised to treat the paediatric population;

(38) ‘paediatric population’ means that part of the population aged between birth and 18 years;

(39) ‘medicinal prescription’ means any medicinal prescription issued by a professional person qualified to do so;

(40) ‘abuse of medicinal products’ means persistent or sporadic, intentional excessive use of medicinal products that is accompanied by harmful physical or psychological effects;

(41) ‘benefit-risk balance’ means an evaluation of the positive therapeutic effects of the medicinal product in relation to the risks referred to in point (35), subpoint (a);

(42) ‘marketing authorisation holder representative’ means the person, commonly known as local representative, designated by the marketing authorisation holder to represent the marketing authorisation holder in the Member State concerned;

(43) ‘package leaflet’ means information for the user that accompanies the medicinal product;

(44) ‘outer packaging’ means the packaging into which is placed the immediate packaging;

(45) ‘immediate packaging’ means the container or other form of packaging immediately in contact with the medicinal product;

(46) ‘labelling’ means information on the immediate packaging or the outer packaging;

(47) ‘name of the medicinal product’ means the name, which may be either an invented name not liable to confusion with the common name, or a common or scientific name accompanied by a trademark or by the name of the marketing authorisation holder;

(48) ‘common name’ means the international non-proprietary name recommended by the World Health Organization for an active substance;

(49) ‘strength of the medicinal product’ means the content of the active substances in a medicinal product, expressed quantitatively per dosage unit, per unit of volume or per unit of weight according to the dosage form;

(50) ‘falsified medicinal product’ means any medicinal product with a false representation of:

(a) its identity, including its packaging and labelling, its name or its composition as regards any of the ingredients including excipients or the strength of those ingredients;

(b) its source, including its manufacturer, its country of manufacturing, its country of origin or its marketing authorisation holder; or

(c) its history, including the records and documents relating to the distribution channels used;

This definition does not include unintentional quality defects and is without prejudice to infringements of intellectual property rights.

(51) 'public health emergency' means a public health emergency recognised at Union level by the Commission under Article 23(1) of Regulation (EU) 2022/2371 of the European Parliament and of the Council[34];

(52) 'entity not engaged in an economic activity' means any legal or natural person that is not engaged in an economic activity and that:

(a) is not an undertaking or controlled by an undertaking; and,

(b) has not concluded any agreements with any undertaking concerning sponsorship or participation to the medicinal product development;

(53) 'micro, small and medium-sized enterprises' means micro, small and medium-sized enterprises as defined in Article 2 of Commission Recommendation 2003/361/EC[35];

(54) 'variation' or 'variation of the terms of a marketing authorisation' means any amendment to:

(a) the contents of the particulars and documents referred to in Article 6(2), Articles 9 to 14 and Article 62, Annex I and Annex II thereto and Article 6 of the [revised Regulation (EC) No 726/2004]; or

(b) the terms of the decision granting the marketing authorisation for a medicinal product, including the summary of product characteristics and any conditions, obligations, or restrictions affecting the marketing authorisation, or changes to the labelling or the package leaflet related to changes to the summary of product characteristics;

(55) 'post-authorisation safety study' means any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures;

(56) 'pharmacovigilance system' means a system used by the marketing authorisation holder and by Member States to fulfil the tasks and responsibilities set out in Chapter IX and designed to monitor the safety of authorised medicinal products and detect any change to their benefit-risk balance;

(57) 'pharmacovigilance system master file' means a detailed description of the pharmacovigilance system used by the marketing authorisation holder with respect to one or more authorised medicinal products;

(58) 'risk management system' means a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to a medicinal product, including the assessment of the effectiveness of those activities and interventions;

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34 Regulation (EU) 2022/2371 of the European Parliament and of the Council of 23 November 2022 on serious cross-border threats to health and repealing Decision No 1082/2013/EU (OJ L 314, 6.12.2022, p. 26).

35 Commission Recommendation of 6 May 2003 concerning the definition of micro, small and medium-sized enterprises (OJ L 124, 20.5.2003, p. 36).

(59) ‘adverse reaction’ means a response to a medicinal product that is noxious and unintended;

(60) ‘serious adverse reaction’ means an adverse reaction that results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or a birth defect;

(61) ‘unexpected adverse reaction’ means an adverse reaction, the nature, severity or outcome of which is not consistent with the summary of product characteristics;

(62) ‘homeopathic medicinal product’ means a medicinal product prepared from homeopathic stocks in accordance with a homeopathic manufacturing procedure described by the European Pharmacopoeia or, in the absence thereof, by the pharmacopoeias currently used officially in the Member States;

(63) ‘traditional herbal medicinal product’ means a herbal medicinal product that fulfils the conditions laid down in Article 134(1);

(64) ‘herbal medicinal product’ means any medicinal product, exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more herbal preparations;

(65) ‘herbal substances’ means all mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried or fresh form, and certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances. Herbal substances are precisely defined by the plant part used and the botanical name according to the binomial system (genus, species, variety and author);

(66) ‘herbal preparations’ means preparations obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation including comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates;

(67) ‘corresponding traditional herbal medicinal product’ means a traditonal herbal medicinal product with the same active substances, irrespective of the excipients used, the same or similar intended purpose, equivalent strength and posology and the same or similar route of administration as the traditional herbal medicinal product applied for;

(68) ‘wholesale distribution of medicinal products’ means all activities, consisting of procuring, holding, supplying or exporting medicinal products, whether for profit or not, apart from supplying medicinal products to the public. Such activities are carried out with manufacturers or their depositories, importers, other wholesale distributors or with pharmacists and persons authorised or entitled to supply medicinal products to the public in the Member State concerned;

(69) ‘brokering of medicinal products’ means all activities in relation to the sale or purchase of medicinal products, except for wholesale distribution, that do not include physical handling and that consist of negotiating independently and on behalf of another legal or natural person;

(70) ‘public service obligation’ means to guarantee permanently an adequate range of medicinal products to meet the requirements of a specific geographical area and to deliver the supplies requested within a very short time over the whole of the area in question.

2. The Commission is empowered to adopt delegated acts in accordance with Article 215 to amend the definitions in paragraph 1, points (2) to (6), (8), (14), (16) to (31), in the light of technical and scientific progress and taking into account definitions agreed at Union and international level without extending the scope of the definitions.

Chapter II
Application requirements for national and centralised marketing authorisations

SECTION 1

GENERAL PROVISIONS

Article 5

Marketing authorisations

1. A medicinal product shall be placed on the market of a Member State only when a marketing authorisation has been granted by the competent authorities of a Member State in accordance with Chapter III (‘national marketing authorisation’) or a marketing authorisation has been granted in accordance with [revised Regulation (EC) No 726/2004] (‘centralised marketing authorisation’).

2. When an initial marketing authorisation has been granted in accordance with paragraph 1, any development concerning the medicinal product covered by the authorisation such as additional therapeutic indication, strengths, pharmaceutical forms, administration routes, presentations, as well as any variations of the marketing authorisation shall also be granted an authorisation in accordance with paragraph 1 or be included in the initial marketing authorisation. All those marketing authorisations shall be considered as belonging to the same global marketing authorisation, in particular for the purpose of the marketing authorisations applications under Articles 9 to 12, including as regards the expiry of the regulatory data protection period for applications using a reference medicinal product.

Article 6

General requirements for marketing authorisation applications

1. In order to obtain a marketing authorisation, an electronic marketing authorisation application shall be submitted to the competent authority concerned in a common format. The Agency shall make available such format after consultation with the Member States.

2. The marketing authorisation application shall include the particulars and documentation listed in Annex I, submitted in accordance with Annex II.

3. The documents and information concerning the results of the pharmaceutical and non-clinical tests and the clinical studies referred to in Annex I shall be accompanied by detailed summaries in accordance with Article 7 and supportive raw data.

4. The risk management system referred to in Annex I shall be proportionate to the identified risks and the potential risks of the medicinal product, and the need for post-authorisation safety data.

5. The marketing authorisation application for a medicinal product that is not authorised in the Union at the time of entry into force of this Directive and for new therapeutic indications, including paediatric indications, new pharmaceutical forms, new strengths and new routes of administration of authorised medicinal products which are protected either by a supplementary protection certificate under [Regulation (EC) No 469/2009 - OP please replace reference by new instrument when adopted], or by a patent which qualifies for the granting of the supplementary protection certificate, shall include one of the following:

   (a) the results of all studies performed and details of all information collected in compliance with an agreed paediatric investigation plan;

   (b) a decision of the Agency granting a product-specific waiver pursuant to Article 75(1) of [revised Regulation No (EC) 726/2004];

   (c) a decision of the Agency granting a class waiver pursuant to Article 75(2) of [revised Regulation No (EC) 726/2004];

   (d) a decision of the Agency granting a deferral pursuant to Article 81 of [revised Regulation No (EC) 726/2004];

   (e) a decision of the Agency taken in consultation with the Commission pursuant to Article 83 of [revised Regulation No (EC) 726/2004] to temporarily derogate from the provision referred to in points (a) to (d) above in case of health emergencies.

   The documents submitted under points (a) to (d) shall, cumulatively, cover all subsets of the paediatric population.

6. The provisions of paragraph 5 shall not apply to medicinal products authorised under Articles 9, 11, 13, Articles 125 to 141 and medicinal products authorised under Articles 10 and 12 which are not protected either by a supplementary protection certificate under [Regulation (EC) No 469/2009 - OP please replace reference by new instrument when adopted], or by a patent which qualifies for the granting of the supplementary protection certificate.

7. The marketing authorisation applicant shall demonstrate that the principle of replacement, reduction and refinement of animal testing for scientific purposes has been applied in compliance with Directive 2010/63/EU with regard to any animal study conducted in support of the application.

   The marketing authorisation applicant shall not carry out animal testing in case scientifically satisfactory non-animal testing methods are available.

Article 7

Expert verification

1. The marketing authorisation applicant shall ensure that the detailed summaries referred to in Article 6(3) have been drawn up and signed by experts with the

necessary technical or professional qualifications before they are submitted to the competent authorities. The technical or professional qualifications of the experts shall be set out in a brief curriculum vitae.

2. The experts referred to in paragraph 1 shall justify any use made of scientific literature under Article 13 in accordance with the requirements set out in Annex II.

Article 8

Medicinal products manufactured outside the Union

Member States shall take all appropriate measures to ensure that:

(a) the competent authorities of the Member States verify that manufacturers and importers of medicinal products coming from third countries are able to carry out manufacture in compliance with the particulars supplied pursuant to Annex I, or to carry out controls according to the methods described in the particulars accompanying the application in accordance with Annex I;

(b) the competent authorities of the Member States may allow manufacturers and importers of medicinal products coming from third countries, in justifiable cases, to have certain stages of manufacture or certain of the controls referred to in point (a) carried out by third parties; in such cases, the verifications by the competent authorities of the Member States shall also be made in the establishment designated.

SECTION 2

SPECIFIC REQUIREMENTS FOR ABRIDGED APPLICATIONS FOR MARKETING AUTHORISATION

Article 9

Applications concerning generic medicinal products

1. By way of derogation from Article 6(2), the applicant for a marketing authorisation for a generic medicinal product shall not be required to provide to the competent authorities the results of non-clinical tests and of clinical studies if equivalence of the generic medicinal product with the reference medicinal product is demonstrated.

2. For the purpose of demonstrating the equivalence as referred to in paragraph 1, the applicant shall submit to the competent authorities equivalence studies, or a justification as to why such studies were not performed, and demonstrate that the generic medicinal product meets the relevant criteria set out in the appropriate detailed guidelines.

3. Paragraph 1 shall also apply if the reference medicinal product has not been authorised in the Member State in which the application for the generic medicinal product is submitted. In this case, the applicant shall indicate in the application the name of the Member State in which the reference medicinal product is or has been authorised. At the request of the competent authority of the Member State in which the application is submitted, the competent authority of the other Member State shall transmit within a period of one month a confirmation that the reference medicinal product is or has been authorised together with the full composition of the reference medicinal product and if necessary, any other relevant documentation.

The various immediate-release oral pharmaceutical forms shall be considered to be the same pharmaceutical form.

4. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety or efficacy. In those cases, the applicant shall submit additional information to demonstrate that the different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance do not differ significantly in respect of those properties.

5. Where there is a significant difference in properties as referred to in paragraph 4, the applicant shall submit additional information in order to prove the safety or efficacy of the different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of the authorised active substance of the reference medicinal product in an application under Article 10.

Article 10

Applications concerning hybrid medicinal products

In cases where the medicinal product does not fall within the definition of a generic medicinal product or has changes in strength, pharmaceutical form, route of administration or therapeutic indications, compared to the reference medicinal product, the results of the appropriate non-clinical tests or clinical studies shall be provided to the competent authorities to the extent necessary to establish a scientific bridge to the data relied upon in the marketing authorisation for the reference medicinal product, and to demonstrate the safety and efficacy profile of the hybrid medicinal product.

Article 11

Applications concerning biosimilar medicinal products

For a biological medicinal product that is similar to a reference biological medicinal product (‘biosimilar medicinal product’), the results of appropriate comparability tests and studies shall be provided to the competent authorities. The type and quantity of supplementary data to be provided must comply with the relevant criteria stated in Annex II and the related detailed guidelines. The results of other tests and studies from the reference medicinal product's dossier shall not be provided.

Article 12

Applications concerning bio-hybrid medicinal products

In cases where a biosimilar medicinal product has changes in strength, pharmaceutical form, route of administration or therapeutic indications, compared to the reference biological medicinal product (‘bio-hybrid’), the results of the appropriate non-clinical tests or clinical studies shall be provided to the competent authorities to the extent necessary to establish a scientific bridge to the data relied upon in the marketing authorisation for the reference biological medicinal product, and to demonstrate the safety or efficacy profile of the biosimilar medicinal product.

Article 13

Applications based on bibliographic data

In cases where no reference medicinal product is or has been authorised for the active substance of the medicinal product concerned, the applicant shall, by way of derogation from Article 6(2), not be required to provide the results of non-clinical tests or clinical studies if the applicant can demonstrate that the active substances of the medicinal product have been in well-established medicinal use within the Union for the same therapeutic use and route of administration and for at least ten years, with recognised efficacy and an acceptable level of safety in terms of the conditions set out in Annex II. In that event, the test and trial results shall be replaced by appropriate bibliographic data in the form of scientific literature.

Article 14

Applications based on consent

Following the granting of a marketing authorisation, the marketing authorisation holder may, by letter of access, allow use to be made of all documentation referred to in Article 6(2) with a view to examining subsequent applications relating to other medicinal products possessing the same qualitative and quantitative composition in terms of active substances and the same pharmaceutical form.

SECTION 3

SPECIFIC REQUIREMENTS FOR APPLICATIONS FOR CERTAIN CATEGORIES OF MEDICINAL PRODUCTS

Article 15

Fixed dose combination medicinal product, platform technologies and multi-medicinal product packages

1. Where justified for therapeutic purposes, a marketing authorisation may be granted for a fixed dose combination medicinal product.

2. Where justified for therapeutic purposes, a marketing authorisation may, in exceptional circumstances, be granted for a medicinal product comprised of a fixed component and a variable component that is pre-defined in order to, where appropriate, target different variants of an infectious agent or, where necessary, to tailor the medicinal product to characteristics of an individual patient or a group of patients (‘platform technology’).

   An applicant that intends to submit an application for a marketing authorisation for such a medicinal product shall seek, in advance, the agreement concerning the submission of such application by the competent authority concerned.

3. Where justified for public health reasons and when the active substances cannot be combined within a fixed dose combination medicinal product, a marketing authorisation may, in exceptional circumstances, be granted to a multi-medicinal product package.

   An applicant that intends to submit a an application for a marketing authorisation for such a medicinal product shall seek, in advance, the agreement concerning the submission of such application by the competent authority concerned.

Article 16

Radiopharmaceuticals

1. A marketing authorisation shall be required for radionuclide generators, kits, and radionuclide precursors, unless they are used as starting material, active substance or intermediate of radiopharmaceuticals covered by a marketing authorisation under Article 5(1).

2. A marketing authorisation shall not be required for a radiopharmaceutical prepared at the time of use by a person or by an establishment authorised, according to national legislation, to use such radiopharmaceutical in an approved healthcare establishment exclusively from authorised radionuclide generators, kits or radionuclide precursors in accordance with the manufacturer's instructions.

Article 17

Antimicrobials

1. Where the application for a marketing authorisation concerns an antimicrobial, the application shall, in addition to the information referred to in Article 6, contain the following:

   (a) an antimicrobial stewardship plan as referred to in Annex I;

   (b) a description of the special information requirements outlined in Article 69 and listed in Annex I.

2. The competent authority may impose obligations on the marketing authorisation holder if it finds the risk mitigation measures contained in the antimicrobial stewardship plan unsatisfactory.

3. The marketing authorisation holder shall ensure that the pack size of the antimicrobial corresponds to the usual posology and duration of treatment.

Article 18

Integral combinations of medicinal products and medical devices

1. For integral combinations of a medicinal product and a medical device the marketing authorisation applicant shall submit data establishing the safe and effective use of the integral combination of the medicinal product and the medical device.

   As part of the assessment, in accordance with Article 29, of the integral combination of a medicinal product and a medical device the competent authorities shall assess the benefit-risk balance of the integral combination of a medicinal product and a medical device, taking into account the suitability of the use of the medicinal product together with the medical device.

2. The relevant general safety and performance requirements set out in Annex I of Regulation (EU) 2017/745 shall apply as far as the safety and performance of the medical device part of the integral combination of a medicinal product with a medical device are concerned.

3. The application for a marketing authorisation for an integral combination of a medicinal product with a medical device shall include the documentation supporting the compliance of the medical device part with the general safety and performance

requirements as referred to in paragraph 2 in accordance with Annex II, including, where relevant, the conformity assessment report by a notified body.

4. In its evaluation of the integral combination of a medicinal product with a medical device concerned, the competent authorities shall recognise the results of the assessment of compliance of the medical device part of that integral combination with the general safety and performance requirements in accordance with Annex I of Regulation (EU) 2017/745 including, where relevant, the results of the assessment by a notified body.

5. The marketing authorisation applicant shall, upon request from the competent authority, submit any additional information related to the medical device and that is relevant for the benefit-risk balance assessment of the integral combination of a medicinal product with a medical device referred to in paragraph 1.

Article 19

Medicinal products in exclusive use with medical devices

1. For medicinal products in exclusive use with a medical device the marketing authorisation applicant shall submit data establishing the safe and effective use of the medicinal product taking into account its use with the medical device.

   As part of the assessment, in accordance with Article 29, of the medicinal product referred to in the first subparagraph, the competent authorities shall assess the benefit-risk balance of the medicinal product taking into account the use of the medicinal product together with the medical device.

2. For medicinal products in exclusive use with a medical device the medical device shall meet the requirements set out in Regulation (EU) 2017/745.

3. The application for a marketing authorisation for a medicinal product in exclusive use with a medical device shall include the documentation supporting the compliance of the medical device with the general safety and performance requirements as referred to in paragraph 2 in accordance with Annex II, including, where relevant, the conformity assessment report by a notified body.

4. In its evaluation of the medicinal product referred to in paragraph 1 the competent authority shall recognise the results of the assessment of compliance of the medical device concerned with the general safety and performance requirements in accordance with Annex I of Regulation (EU) 2017/745 including, where relevant, the results of the assessment by a notified body.

5. The marketing authorisation applicant shall, upon request from the competent authority, submit any additional information related to the medical device and that is relevant for the benefit-risk balance assessment of the medicinal product referred to in paragraph 1, taking into account the use of the medicinal product with the medical device.

6. If the action of the medicinal product is not ancillary to that of the medical device, the medicinal product shall comply with the requirements of this Directive and of the [revised Regulation (EC) No 726/2004], taking into account its use with the medical device, without prejudice to the specific requirements of the Regulation (EU) 2017/745.

In this case, the marketing authorisation applicant shall, upon request from the competent authorities, submit any additional information related to the medical device, taking into account its use with the medicinal product and that is relevant for the post-authorisation monitoring of the medicinal product, without prejudice to the specific requirements of the [revised Regulation (EC) No 726/2004].

Article 20

Combinations of medicinal products with products other than medical devices

1. For combinations of a medicinal product with a product other than a medical device, the marketing authorisation applicant shall submit data establishing the safe and effective use of the combination of the medicinal product and the other product.

   As part of the assessment, in accordance with Article 29, of the combination of a medicinal product with a product other than a medical device the competent authority shall assess the benefit-risk balance of the combination of a medicinal product and a product other than a medical device, taking into account the use of the medicinal product together with the other product.

2. The marketing authorisation applicant shall, upon request from the competent authority submit any additional information related to the product other than medical devices and that is relevant for the benefit-risk balance assessment of the combination of medicinal products with the product other than medical devices, taking into account the suitability of the use of the medicinal product with the product referred to in paragraph 1.

SECTION 4

SPECIFIC DOSSIER REQUIREMENTS

Article 21

Risk management plan

The applicant of a marketing authorisation for a medicinal product referred to in Articles 9 and 11 shall not be required to submit a risk management plan and a summary thereof, provided that no additional risk minimisation measures exist for the reference medicinal product and provided that the marketing authorisation for the reference medicinal product has not been withdrawn prior to the submission of the application.

Article 22

Environmental risk assessment and other environmental information

1. When preparing the environmental risk assessment (‘ERA’) to be submitted pursuant to Article 6(2), the applicant shall take into account the scientific guidelines on the environmental risk assessment of medicinal products for human use as referred to in paragraph 6, or provide the reasons for any divergence from the scientific guidelines to the Agency or, as appropriate to the competent authority of the Member State concerned, in a timely manner. Where available, the applicant shall take into account existing ERAs performed under other Union legislation.

2. The ERA shall indicate whether the medicinal product or any of its ingredients or other constituents is one of the following substances according to the criteria of Annex I to the Regulation (EC) No 1272/2008:

(a) persistent, bioaccumulative and toxic (PBT);

(b) very persistent and very bioaccumulative (vPvB);

(c) persistent, mobile and toxic (PMT), very persistent and very mobile (vPvM);

or are endocrine active agents.

3. The applicant shall also include in the ERA risk mitigation measures to avoid or where it is not possible, limit emissions to air, water and soil of pollutants listed in Directive 2000/60/EC, Directive 2006/118/EC, Directive 2008/105/EC and Directive 2010/75/EU. The applicant shall provide detailed explanation that the proposed mitigation measures are appropriate and sufficient to address the identified risks to the environment.

4. The ERA for antimicrobials shall include an evaluation of the risk for antimicrobial resistance selection in the environment due to the entire manufacturing supply chain inside and outside the Union, use and disposal of the antimicrobial taking into account, where relevant, the existing international standards that have established predicted no effect concentration (PNECs) specific for antibiotics.

5. The Agency shall draw up scientific guidelines in accordance with Article 138 of [revised Regulation No (EC) 726/2004], to specify technical details regarding the ERA requirements for medicinal products for human use. Where appropriate, the Agency shall consult the European Chemical Agency (ECHA), the European Food Safety Authority (EFSA) and the European Environmental Agency (EEA) on the drafting of these scientific guidelines.

6. The marketing authorisation holder shall update the ERA with new information without undue delay to the relevant competent authorities, in accordance with Article 90(2), if new information pertaining to the assessment criteria referred to in Article 29 becomes available and could lead to a change of the conclusions of the ERA. The update shall include any relevant information from environmental monitoring, including monitoring under Directive 2000/60/EC, from eco-toxicity studies, from new or updated risk assessments under other Union legislation, as referred to in paragraph 1, and environmental exposure data.

   For an ERA conducted prior to [OP please insert the date = 18 months after the date of entering into force of this Directive], the competent authority shall request the marketing authorisation holder to update the ERA if missing information has been identified for medicinal products potentially harmful to the environment.

7. For medicinal products referred to in Articles 9 to 12, the applicant may refer to ERA studies conducted for the reference medicinal product when preparing the ERA.

Article 23

ERA of medicinal products authorised before 30 October 2005

1. By [OP please insert the date = 30 months after the date of the entry into force of this Directive] the Agency shall, after consultation with the competent authorities of the Member States, the European Chemical Agency (ECHA), the European Food Safety Authority (EFSA) and the European Environmental Agency (EEA), establish a

programme for the ERA to be submitted in accordance with Article 22 of the medicinal products authorised before 30 October 2005 that have not been subject to any ERA and that the Agency has identified as potentially harmful to the environment in accordance with paragraph 2.

This programme shall be made publicly available by the Agency.

2. The Agency shall set the scientific criteria for the identification of the medicinal products as potentially harmful to the environment and for the prioritisation of their ERA, using a risk based approach. For this task, the Agency may request from marketing authorisation holders the submission of relevant data or information.

3. The marketing authorisation holders for medicinal products identified in the programme referred to in paragraph 1 shall submit the ERA to the Agency. The outcome of the assessment of the ERA including the data submitted by the marketing authorisation holder shall be made publicly available by the Agency.

4. Where there are several medicinal products identified in the programme referred to in paragraph 1 that contain the same active substance and that are expected to pose the same risks to the environment, the competent authorities of the Member States or the Agency shall encourage the marketing authorisation holders to conduct joint studies for the ERA, to minimise unnecessary duplication of data and use of animals.

Article 24

System of ERA monographs of the ERA data of active substances

1. The Agency shall, in collaboration with the competent authorities of the Member States, set-up an active substance based review system of ERA data ('ERA monographs') for authorised medicinal products. An ERA monograph shall include a comprehensive set of physiochemical data, fate data and effect data based on an assessment of a competent authority.

2. The setting-up of the system of ERA monographs shall be based on a risk-based prioritisation of active substances.

3. In the preparation of the ERA monograph referred to in paragraph 1, the Agency may request information, studies and data from competent authorities of the Member States and from marketing authorisation holders.

4. The Agency in cooperation with the competent authorities of the Member States shall conduct a proof-of-concept pilot of ERA monographs to be completed within three years after entering into force of this Directive.

5. The Commission is empowered to adopt delegated acts in accordance with Article 215 and based on the results of a proof-of-concept pilot referred to in paragraph 4, to supplement this Directive by specifying the following:

   (a) the content and format of ERA monographs;

   (b) the procedures for adopting and updating the ERA monographs;

   (c) the procedures for submission of information, studies and data referred to in paragraph 3;

   (d) the risk-based prioritisation criteria for the selection and prioritisation referred to in paragraph 2;

(e) the use of ERA monographs in the context of new marketing authorisation applications for medicinal products to support their ERA.

Article 25

Active substance master file certificate

1. Marketing authorisation applicants may, instead of submitting the relevant data on a chemical active substance of a medicinal product required in accordance with Annex II, rely on an active substance master file, an active substance master file certificate granted by the Agency in accordance with this Article ('active substance master file certificate') or a certificate confirming that the quality of the active substance concerned is suitably controlled by the relevant monograph of the European Pharmacopeia.

   Marketing authorisation applicants may only rely on an active substance master file if no certificate exists on the same active substance master file.

2. An active substance master file certificate may be granted by the Agency in cases where the relevant data on the active substance concerned is not already covered by a monograph of the European Pharmacopeia or by an active substance master file certificate.

   In order to obtain an active substance master file certificate, an application shall be submitted to the Agency. The applicant for an active substance master file certificate shall demonstrate that the active substance concerned is not already covered by a monograph of the European Pharmacopeia or an active substance master file certificate. The Agency shall examine the application and, in case of a positive outcome, shall grant the certificate that shall be valid throughout the Union. In case of centralised marketing authorisations, the application for an active substance master file certificate may be submitted as part of the marketing authorisation application for the corresponding medicinal product.

   The Agency shall establish a repository of active substance master files, their assessments reports and their certificates and ensure that personal data is protected. The Agency shall ensure that the competent authorities of the Member State have access to this repository.

3. The active substance master file and the active substance master file certificate shall cover all the information required in Annex II on the active substance.

4. The active substance master file certificate holder shall be the manufacturer of the active substance.

5. The active substance master file certificate holder shall keep the active substance master file up to date with scientific and technological progress and introduce the changes required to ensure that the active substance is manufactured and controlled in accordance with generally accepted scientific methods.

6. If requested by the Agency, the manufacturer of the substance for which an application for an active substance master file certificate has been submitted or the active substance master file certificate holder shall undergo an inspection to verify the information contained in the application or the active substance master file or their compliance with good manufacturing practices for active substances referred to in Article 160.

If the manufacturer of an active substance refuses to undergo such an inspection, the Agency may suspend or terminate the application for an active substance master file certificate.

7. If the active substance master file certificate holder does not fulfil the obligations set out in the paragraphs 5 and 6, the Agency may suspend or withdraw the certificate and, the competent authorities of the Member States may suspend or revoke the marketing authorisation of a medicinal product relying on that certificate or take measures to prohibit the supply of the medicinal product relying on that certificate.

8. The marketing authorisation holder of the medicinal product granted on the basis of an active substance master file certificate remains responsible and liable for that medicinal product.

9. The Commission is empowered to adopt delegated acts in accordance with Article 215 to supplement this Directive by specifying, the following:

(a) the rules governing the content and format of the application for an active substance master file certificate;

(b) the rules for the examination of an application for an active substance master file certificate and for the granting of the certificate;

(c) the rules for making publicly available of active substance master file certificates;

(d) the rules for introducing changes to the active substance master file and the active substance master file certificate;

(e) the rules on access for competent authorities of the Member States to the active substance master file and its assessment report;

(f) the rules on access for marketing authorisation applicants and marketing authorisation holders relying on an active substance master file certificate to the active substance master file and to the assessment report.

Article 26

Additional quality master files

1. Marketing authorisation applicants may, instead of submitting the relevant data on an active substance other than a chemical active substance, or on other substances present or used in the manufacture of a medicinal product, required in accordance with Annex II, rely on an additional quality master file, an additional quality master file certificate granted by the Agency in accordance with this Article (‘additional quality master file certificate’), or a certificate confirming that the quality of that substance is suitably controlled by the relevant monograph of the European Pharmacopeia.

Marketing authorisation applicants may only rely on an additional quality master file certificate if no certificate exists on the same additional quality master file.

2. Article 25, paragraphs 1 to 5, 7 and 8 shall also apply *mutadis mutandis* to additional quality master file certification.

3. The Commission is empowered to adopt delegated acts in accordance with Article 215 to supplement this Directive by specifying:

(a) the rules governing the content and format of the application for an active substance master file certificate;

(b) additional quality master files for which a certificate may be used in order to provide specific information on the quality of a substance present or used in the manufacture of a medicinal product;

(c) the rules for the examination of applications for making publicly available of additional quality master file certificates;

(d) the rules for introducing changes to the additional quality master file and the certificate;

(e) the rules on access for competent authorities of the Member State to the additional quality master file and its assessment report;

(f) the rules on access for marketing authorisation applicants and marketing authorisation holders relying on an additional quality master file certificate to the additional quality master file and to the assessment report.

4. If requested by the Agency, the manufacturer of a substance present or used in the manufacture of a medicinal product for which an application for an additional quality master file certificate has been submitted or the additional quality master file certificate holder shall undergo an inspection to verify the information contained in the application or the quality master file.

If the manufacturer of this substance refuses to undergo such an inspection, the Agency may suspend or terminate the application for the additional quality master file certificate.

Article 27

Excipients

1. The applicant shall provide information on the excipients used in a medicinal product in accordance with the requirements set out in Annex II.

Excipients shall be examined by the competent authorities as part of the medicinal product.

2. Colours shall be used in medicinal products only if they are included in one of the following lists:

(a) the Union list of authorised food additives in Table 1 in Part B of Annex II to Regulation (EC) No 1333/2008 and comply with the purity criteria and specifications laid down in Commission Regulation (EU) No 231/2012;

(b) the list established by the Commission pursuant to paragraph 3.

3. The Commission may establish a list of colours permitted for use in medicinal products other than those included in the Union list of authorised food additives.

The Commission shall, where applicable on the basis of an opinion of the Agency, adopt a decision whether the colour concerned shall be added to list of colours permitted for use in medicinal products referred to in the first subparagraph.

A colour may be added to the list of colours permitted for use in medicinal products only where the colour has been removed from the Union list of authorised food additives.

Where relevant, the list of colours permitted for use in medicinal products shall include purity criteria, specifications or restrictions applicable to the colours included in that list.

The list of colours permitted for use in medicinal products shall be established by way of implementing acts. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 214(2).

4. If a colour used in medicinal product is removed from the Union list of authorised food additives, on the basis of the scientific opinion of the European Food Safety Authority ('EFSA'), the Agency shall, on the request of the Commission or on its own initiative, without undue delay issue a scientific opinion as regards the use of the colour concerned in medicinal product, taking into account the opinion of the EFSA if relevant. The opinion of the Agency shall be adopted by the Committee for Medicinal Products for Human Use.

   The Agency without undue delay shall send to the Commission its scientific opinion on the use of the colour in medicinal product together with a report on the assessment.

   The Commission shall, on the basis of the Agency opinion, and without undue delay, decide whether the colour concerned can be used in medicinal products and, where applicable, include it in the list of colours permitted for use in medicinal products referred to in paragraph 3.

5. If a colour has been removed from the Union list of authorised food additives for reasons that do not require an EFSA opinion, the Commission shall decide on the use of the colour concerned in medicinal products and, where applicable, include it in the list of colours permitted for use in medicinal products referred to in paragraph 3. The Commission may, in such cases, request the opinion from the Agency.

6. A colour that has been removed from the Union list of authorised food additives can still be used as a colour in medicinal products until the Commission takes the decision on whether to include the colour on the list of colours permitted for use in medicinal products in accordance with paragraph 3.

7. Paragraphs 2 to 6 shall also apply to colours used in veterinary medicinal products as defined in Article 4(1) of Regulation (EU) 2019/6 of the European Parliament and of the Council [36].

SECTION 5

ADAPTED DOSSIER REQUIREMENTS

Article 28

Adapted frameworks due to the characteristics or methods inherent to the medicinal product

1. Medicinal products listed in Annex VII shall be subject to specific scientific or regulatory requirements due to the characteristics or methods inherent to the medicinal product, when:

[36] Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC.

(a) it is not possible to adequately assess the medicinal product or category of medicinal products applying the applicable requirements due to scientific or regulatory challenges arising from characteristics or methods inherent to the medicinal product; and

(b) the characteristics or methods positively impact the quality, safety and efficacy of the medicinal product or category of medicinal product or provide a major contribution to patient access or patient care.

2. The Commission is empowered to adopt delegated acts in accordance with Article 215 to amend Annex VII in order to take account of scientific and technical progress.

3. The Commission is empowered to adopt delegated acts in accordance with Article 215 to supplement this Directive by laying down:

(a) detailed rules for the marketing authorisation and supervision of the medicinal products referred to in paragraph 1;

(b) the technical documentation to be submitted by applicants for marketing authorisations for medicinal products referred to in paragraph 1.

4. The detailed rules referred to in paragraph 3, point (a), shall be proportionate to the risk and impact involved. These may entail adapted, enhanced, waived or deferred requirements. Any waiver or deferral shall be limited to the extent strictly necessary, proportionate and duly justified by the characteristics or methods inherent to the medicinal product, and shall be regularly reviewed and evaluated. Apart from the detailed rules referred to in paragraph 3, point (a), all other rules laid out in this Directive shall apply.

5. Until the adoption of detailed rules for specific medicinal products listed in Annex VII pursuant to paragraph 3, an application for a marketing authorisation for that medicinal product may be submitted in accordance with Article 6(2).

6. When adopting delegated acts referred to in this Article, the Commission shall take into account any available information resulting from a regulatory sandbox established in accordance with Article 115 of the [revised Regulation (EC) No 726/2004].

Chapter III
Procedures for national marketing authorisations

SECTION 1

GENERAL PROVISIONS

Article 29

Examination of marketing authorisation application

1. In order to examine an application submitted in accordance with Articles 6 and 9 to 14, the competent authority of the Member State:

(a) shall verify whether the particulars and documentations submitted in support of the application comply with Articles 6 and 9 to 14 (‘validation’), and examine

whether the conditions for issuing a marketing authorisation set out in Articles 43 to 45 are complied with;

(b) may submit the medicinal product, its starting materials or ingredients and, if need be, its intermediate products or other, for testing by an Official Medicines Control Laboratory or a laboratory that a Member State has designated for that purpose in order to ensure that the control methods employed by the manufacturer of medicinal products and described in the particulars accompanying the application in accordance with Annex I are satisfactory;

(c) may, where appropriate, require the applicant to supplement the particulars accompanying the application in respect of the items listed in the Articles 6 and 9 to 14;

(d) may consider and decide upon additional evidence available, independently from the data submitted by the marketing authorisation applicant.

2. Where the competent authority of the Member State avails itself of the option referred to in the first subparagraph, point (c), the time limits laid down in Article 30 shall be suspended until such time as the supplementary information required has been provided or for the time allowed to the applicant for giving oral or written explanations.

3. Where the competent authority of the Member State considers that the marketing authorisation application is incomplete, or contains critical deficiencies that may prevent the evaluation of the medicinal product it shall inform the applicant accordingly and shall set a time limit for submitting the missing information and documentation. If the applicant fails to provide the missing information and documentation within the time limit set, the application shall be considered to have been withdrawn.

4. In cases where on examination of an application for a marketing authorisation the competent authority of the Member State considers that the submitted data are not of sufficient quality or maturity for the completion of the examination of the application, the examination can be terminated within 90 days of the validation of the application.

The competent authority of the Member State shall summarise the deficiencies in writing. On this basis, the competent authority of the Member State shall inform the applicant accordingly and set a time limit to address the deficiencies. The application shall be suspended until the applicant addresses the deficiencies. If the applicant fails to address those deficiencies within the time limit set by the competent authority of the Member State, the application shall be considered as withdrawn.

Article 30

Duration of examination of marketing authorisation application

Member States shall take all appropriate measures to ensure that the procedure for granting a marketing authorisation for medicinal products is completed within a maximum of 180 days after the submission of a valid application from the date of validation of a marketing authorisation application.

Article 31

Types of national marketing authorisation procedures

National marketing authorisations may be granted in accordance with the procedures laid down in Article 32 (‘purely national marketing authorisation procedure’), Articles 33 and 34 (‘decentralised procedure for national marketing authorisation’) or Articles 35 and 36 (‘mutual recognition procedure for national marketing authorisation’).

SECTION 2

MARKETING AUTHORISATIONS VALID IN A SINGLE MEMBER STATE

Article 32

Purely national marketing authorisation procedure

1. An application for marketing authorisation according to Article 6(2) under the purely national marketing authorisation procedure shall be submitted to the competent authority in that Member State in which the marketing authorisation is applied.

2. The competent authority in the Member State concerned shall examine the application in accordance with Articles 29 and 30 and grant a marketing authorisation in accordance with Articles 43 to 45 and applicable national provisions.

3. A marketing authorisation granted under the purely national marketing authorisation procedure shall be valid only in the Member State of the competent authority that granted it.

SECTION 3

MARKETING AUTHORISATIONS VALID IN SEVERAL MEMBER STATES

Article 33

Scope of decentralised procedure for national marketing authorisations

1. An application for marketing authorisation under the decentralised procedure for national marketing authorisation in several Member States in respect of the same medicinal product shall be submitted to the competent authorities in those Member States in which the marketing authorisation is applied.

2. The competent authorities in the Member State concerned shall examine the applications in accordance with Articles 29, 30 and 34 and grant a marketing authorisation in accordance with Articles 43 to 45.

3. Where a competent authority of the Member State notes that another marketing authorisation application for the same medicinal product is being examined by the competent authority in another Member State, the competent authorities of the Member States concerned shall decline to examine the application and shall advise the applicant that the provisions referred to in Articles 35 and 36 apply.

4. Where the competent authorities of the Member States are informed that another Member State has authorised a medicinal product that is the subject of a marketing authorisation application in the Member State concerned, they shall reject the application unless it was submitted in compliance with the provisions referred to in Articles 35 and 36.

5. Marketing authorisations granted under decentralised procedure for national marketing authorisation shall be valid only in those Member States of the competent authority that granted it.

Article 34

Decentralised procedure for national marketing authorisations

1. With a view to obtain a national marketing authorisation for a medicinal product in several Member States in respect of the same medicinal product under the decentralised procedure for national marketing authorisation, an applicant shall submit a marketing authorisation application based on an identical dossier to the competent authority of the Member State chosen by the applicant, to prepare an assessment report on the medicinal product in accordance with Article 43(5) and to act in accordance with this Section ('reference Member State for the decentralised procedure'), and to the competent authorities in the other Member States concerned.

2. The application for marketing authorisation shall contain:

   (a) the particulars and documentations referred to Articles 6, 9 to 14 and 62;

   (b) a list of Member States concerned by the application.

3. The applicant shall inform all the competent authorities of all Member States of its application at the time of submission. The competent authority of a Member State may request for justified public health reasons to enter the procedure and shall inform the applicant and the competent authority of the reference Member State for the decentralised procedure of its request within 30 days from the date of submission of the application. The applicant shall provide the competent authorities of those Member States entering the procedure with the application without undue delay.

4. In cases where on examination of an application for a marketing authorisation the competent authority of the reference Member State for the decentralised procedure considers that the submitted data are not of sufficient quality or maturity for the completion of the examination of the application, the examination can be terminated within 90 days of the validation of the application.

   The competent authority of the reference Member State for the decentralised procedure shall summarise the deficiencies in writing. On this basis, the competent authority of the reference Member State for the decentralised procedure shall inform the applicant and the competent authorities of the Member States concerned accordingly and set a time limit to address the deficiencies. The application shall be suspended until the applicant addresses the deficiencies. If the applicant fails to address those deficiencies within the time limit set by the competent authority of the reference Member State for the decentralised procedure, the application shall be considered as withdrawn.

   The competent authority of the reference Member State for the decentralised procedure shall inform the competent authorities of the Member States concerned and the applicant accordingly.

5. Within 120 days after validation of the application, the competent authority of the reference Member State for the decentralised procedure shall prepare an assessment report, a summary of product characteristics, the labelling and the package leaflet and shall send them to the Member States concerned and to the applicant.

6. Within 60 days of receipt of the assessment report, the competent authorities of the Member States concerned shall approve the assessment report, the summary of product characteristics and the labelling and package leaflet and shall inform the competent authority of the reference Member State for the decentralised procedure accordingly. The competent authority of the reference Member State for the decentralised procedure shall record the agreement of all parties, close the procedure and inform the applicant accordingly.

7. Within 30 days after acknowledgement of the agreement, the competent authorities of all Member States concerned in which an application has been submitted in accordance with paragraph 1 shall adopt a decision according to Articles 43 to 45 and in conformity with the approved assessment report, the summary of product characteristics and the labelling and package leaflet as approved.

SECTION 4

MUTUAL RECOGNITION OF NATIONAL MARKETING AUTHORISATIONS

Article 35

Scope of mutual recognition procedure for national marketing authorisations

An application for marketing authorisation for mutual recognition procedure for national marketing authorisation, granted under Articles 43 to 45 and in accordance with Article 32, shall be submitted to the competent authorities of other Member States in accordance with the procedure laid down in Article 36.

Article 36

Mutual recognition procedure for national marketing authorisations

1. An application for mutual recognition of a marketing authorisation, granted under Articles 43 to 45 and in accordance with Article 32, in several Member States in respect of the same medicinal product shall be submitted to the competent authority of the Member State that granted the marketing authorisation ('reference Member State for the mutual recognition procedure') and to the competent authorities of the Member States concerned where the applicant seeks to obtain a national marketing authorisation.

2. Application shall include a list of Member States concerned by the application.

3. The competent authority of the reference Member State for the mutual recognition procedure shall reject an application for mutual recognition of marketing authorisation of medicinal product within a year from the granting of that marketing authorisation, unless the competent authority of the Member State informs the competent authority of the reference Member State for the mutual recognition procedure of its interest in this medicinal product.

4. The applicant shall inform the competent authorities of all Member States of its application at the time of submission. The competent authority of a Member State may request for justified public health reasons to enter the procedure and shall inform the applicant and the competent authority of the reference Member State for the mutual recognition procedure of its request within 30 days from the date of submission of the application. The applicant shall provide the competent authorities

of those Member States entering the procedure with the application without undue delay.

5. If the competent authorities of the Member States concerned so require, the marketing authorisation holder shall request the competent authority of the reference Member State for the mutual recognition procedure to update the assessment report drawn on the medicinal concerned by the application. In that case, the reference Member State shall update the assessment report within 90 days after validation of the application. If the competent authorities of the Member States concerned do not require the update of the assessment report, the reference Member State shall provide the assessment report within 30 days.

6. Within 60 days of receipt of the assessment report, the competent authorities of the Member States concerned shall approve the assessment report, the summary of product characteristics, the labelling and package leaflet and shall inform the competent authority of the reference Member State accordingly.

7. The competent authority of reference Member State for the mutual recognition procedure shall record the agreement of all parties, close the procedure and inform the applicant accordingly. The assessment report together with the summary of product characteristics, labelling and package leaflet approved by the competent authority of the reference Member State for the mutual recognition procedure shall be sent to the Member States concerned and to the applicant.

8. Within 30 days after acknowledgement of the agreement, the competent authorities of all Member States concerned in which an application has been submitted in accordance with paragraph 1 shall adopt a decision according to Articles 43 to 45 in conformity with the approved assessment report, the summary of product characteristics, the labelling and package leaflet as approved.

SECTION 5

COORDINATION OF NATIONAL MARKETING AUTHORISATION

Article 37

Coordination group for decentralised and mutual recognition procedures

1. A coordination group for decentralised and mutual recognition procedures (‘coordination group’) shall be set up for the following purposes:

   (a) the examination of any question relating to a national marketing authorisation of a medicinal product in two or more Member States in accordance with the procedures laid down in Sections 3, 4 and 5 of this Chapter, and Article 95;

   (b) the examination of questions related to the pharmacovigilance of medicinal products covered by national marketing authorisations, in accordance with Articles 108, 110, 112, 116 and 121;

   (c) the examination of questions relating to variations of national marketing authorisations, in accordance with Article 93(1).

   For the fulfilment of its pharmacovigilance tasks contemplated under first subparagraph, point (b), including approving risk management systems and monitoring their effectiveness, the coordination group shall rely on the scientific

assessment and the recommendations of the Pharmacovigilance Risk Assessment Committee referred to in Article 149 of [revised Regulation (EC) No 726/2004].

2. The coordination group shall be composed of one representative per Member State appointed for a renewable period of three years. Member States may appoint an alternate for a renewable period of three years. Members of the coordination group may arrange to be accompanied by experts.

   Members of the coordination group and experts shall, for the fulfilment of their tasks, rely on the scientific and regulatory resources available to competent authorities of the Member States. Each competent authority of the Member State shall monitor the level of expertise of the evaluations carried out and facilitate the activities of nominated coordination group members and experts.

   Article 147 of [revised Regulation (EC) No 726/2004] shall apply to the coordination group as regards transparency and the independence of its members.

3. The Agency shall provide the secretariat of this coordination group. The coordination group shall draw up its own Rules of Procedure, which shall enter into force after a favourable opinion has been given by the Commission. These Rules of Procedure shall be made publicly available.

4. The Executive Director of the Agency or the representative of the Executive Director and representatives of the Commission shall be entitled to attend all meetings of the coordination group.

5. The members of the coordination group shall ensure that there is appropriate coordination between the tasks of that group and the work of competent authorities of the Member States, including the consultative bodies concerned with the marketing authorisation.

6. Where otherwise provided for in this Directive, within the coordination group, all Member States representatives shall use their best endeavours to reach a position by consensus on the action to be taken. If such a consensus cannot be reached, the position of the majority of the Member States represented within the coordination group shall prevail.

7. Members of the coordination group shall be required, even after their duties have ceased, not to disclose information of the kind covered by the obligation of professional secrecy.

Article 38

Divergent positions of Member States in decentralised or mutual recognition procedure

1. If, at the end of the period laid down in Articles 34(6) or 36(6), there is disagreement between Member States on whether the marketing authorisation can be issued, on the grounds of potential serious risk to public health, the disagreeing Member State concerned shall give a detailed explanation of the points of disagreement and the reasons for its position to the reference Member State, to the other Member States concerned and to the applicant. The points of disagreement shall be referred to the coordination group without undue delay.

2. Guidelines to be adopted by the Commission shall define a potential serious risk to public health.

3. Within the coordination group, all disagreeing Member States concerned shall use their best endeavours to reach agreement on the action to be taken. They shall allow the applicant the opportunity to make its point of view known orally or in writing. If, within 60 days of the communication of the points of disagreement, the Member States reach an agreement by consensus, the reference Member State shall record the agreement, close the procedure and inform the applicant accordingly. The procedure laid down in Articles 34(7) or 36(8) shall apply.

4. If within the 60-day period laid down in paragraph 3, an agreement by consensus cannot be reached, the position of the majority of the Member States represented within the coordination group shall be forwarded to the Commission, which shall apply the procedure laid down in Articles 41 and 42.

5. In the circumstances referred to in paragraph 4, Member States that have approved the assessment report, the summary of product characteristics, the labelling and package leaflet of the reference Member State may, at the request of the applicant, authorise the medicinal product without waiting for the outcome of the procedure laid down in Article 41. In that event, the national marketing authorisation granted shall be without prejudice to the outcome of that procedure.

Article 39

Referral procedure of divergent decisions of Member States

If applications for a national marketing authorisation have been submitted in accordance with Articles 6 and 9 to 14 for a particular medicinal product, and if Member States have adopted divergent decisions concerning the national marketing authorisation, its variation, suspension or revocation or the summary of product characteristics, the competent authority of the Member State, the Commission or the marketing authorisation holder may refer the matter to the Committee for Medicinal Products for Human Use for the application of the procedure laid down in Articles 41 and 42.

Article 40

Harmonisation of summary of product characteristics

1. In order to promote the harmonisation of national marketing authorisations for medicinal products throughout the Union, the competent authorities of the Member States shall, each year, forward to the coordination group referred to in Article 37 a list of medicinal products for which a harmonised summary of product characteristics is to be drawn up.

2. The coordination group shall lay down a list of medicinal products for which a harmonised summary of product characteristics is to be drawn up, taking into account the proposals from the competent authorities of all Member States, and shall forward that list to the Commission.

3. The Commission or the competent authority of a Member State, in agreement with the Agency and taking into account the views of interested parties, may refer the matter concerning the harmonisation of summary of products characteristics of those medicinal products to the Committee for Medicinal Products for Human Use for the application of the procedure laid down in Articles 41 and 42.

Article 41

Scientific evaluation by the Committee for Medicinal Products for Human Use in a referral procedure

1. When reference is made to the procedure laid down in this Article, the Committee for Medicinal Products for Human Use referred to in Article 148 of [revised Regulation (EC) No 726/2004] shall consider the matter concerned and shall issue a reasoned opinion within 60 days from the date when the matter was referred to it.

   However, in cases submitted to the Committee for Medicinal Products for Human Use in accordance with Articles 39, 40 and 95, this period may be extended by the Committee for Medicinal Products for Human Use for a further period of up to 90 days.

   On a proposal from its chairperson, the Committee for Medicinal Products for Human Use may agree to a shorter deadline.

2. In order to consider the matter, the Committee for Medicinal Products for Human Use shall appoint one of its members to act as rapporteur. The Committee may also appoint individual experts to advise it on specific questions. When appointing experts, the Committee for Medicinal Products for Human Use shall define their tasks and specify the time limit for the completion of these tasks.

3. Before issuing its opinion, the Committee for Medicinal Products for Human Use shall provide the applicant or the marketing authorisation holder with an opportunity to present written or oral explanations within a time limit which it shall specify.

   The opinion of the Committee for Medicinal Products for Human Use shall be accompanied by a summary of product characteristics, the labelling and package leaflet.

   If necessary, the Committee for Medicinal Products for Human Use may call upon any other person to provide information relating to the matter before it or consider a public hearing.

   The Agency shall, in consultation with the parties concerned, draw up Rules of Procedure on the organisation and conduct of public hearings, in accordance with Article 163 of [revised Regulation (EC) No 726/2004].

   The Committee for Medicinal Products for Human Use may suspend the time limits referred to in paragraph 1 in order to allow the applicant or the marketing authorisation holder to prepare explanations.

4. The Agency shall without undue delay inform the applicant or the marketing authorisation holder where the opinion of the Committee for Medicinal Products for Human Use provides that:

   (a) the application does not satisfy the criteria for a marketing authorisation;

   (b) the summary of product characteristics proposed by the applicant or the marketing authorisation holder in accordance with Article 62 is to be amended;

   (c) the marketing authorisation is to be granted subject to certain conditions, that are considered essential for the safe and effective use of the medicinal product, including pharmacovigilance;

   (d) a marketing authorisation is to be suspended, varied or revoked;

(e) the medicinal product satisfies the conditions set out in Article 83 regarding medicinal products addressing an unmet medical need.

Within 12 days after receipt of the opinion, the applicant or the marketing authorisation holder may notify the Agency in writing of its intention to request a re-examination of the opinion. In that case, they shall forward to the Agency the detailed grounds for the request within 60 days after receipt of the opinion.

Within 60 days following receipt of the grounds for the request, the Committee for Medicinal Products for Human Use shall re-examine its opinion in accordance with Article 12(2), third subparagraph, of [revised Regulation (EC) No 726/2004]. The reasons for the conclusion reached further to its re-examination shall be annexed to the assessment report referred to in Article 12(2), third subparagraph, of [revised Regulation (EC) No 726/2004].

5. Within 12 days after its adoption, the Agency shall forward the final opinion of the Committee for Medicinal Products for Human Use to the competent authorities of the Member States, to the Commission and to the applicant or the marketing authorisation holder, together with a report describing the assessment of the medicinal product and stating the reasons for its conclusions.

In the event of an opinion in favour of granting or maintaining a marketing authorisation to place the medicinal product concerned on the market, the following documents shall be annexed to the final opinion:

(a) a summary of product characteristics, as referred to in Article 62;

(b) the details of any conditions affecting the marketing authorisation within the meaning of paragraph 4, first subparagraph, point (c);

(c) the details of any recommended conditions or restrictions with regard to the safe and effective use of the medicinal product;

(d) the labelling and package leaflet.

Article 42

Commission decision

1. Within 12 days of receipt of the opinion of the Committee for Medicinal Products for Human Use, the Commission shall submit to the Standing Committee on Medicinal Products for Human Use referred to in Article 214(1) a draft of the decision on the application, on the basis of the requirements set out in this Directive.

In duly justified cases, the Commission may return the opinion to the Agency for further consideration.

Where a draft decision envisages the granting of a marketing authorisation, it shall include or make reference to the documents referred to in Article 41(5), second subparagraph.

Where a draft decision differs from the opinion of the Agency, the Commission shall provide a detailed explanation of the reasons for the differences.

The Commission shall send the draft decision to the competent authorities of the Member States and the applicant or the marketing authorisation holder.

2. The Commission shall, by means of implementing acts, adopt a final decision within 12 days after obtaining the opinion of the Standing Committee on Medicinal Products for Human Use.

Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 214(2) and (3).

3. Where a Member State raises important new questions of a scientific or technical nature that have not been addressed in the opinion delivered by the Agency, the Commission may refer the application back to the Agency for further consideration. In that case, the procedures set out in paragraphs 1 and 2 shall start again upon reception of the reply of the Agency.

4. The decision referred to in paragraph 2 shall be addressed to all Member States and forwarded for information to the applicant or the marketing authorisation holder. The Member States concerned and the reference Member State shall adopt a decision to either grant or revoke the marketing authorisation, or vary its terms as necessary to comply with the decision referred to in paragraph 2 within 30 days following its notification. In the decision to grant, suspend, revoke or vary the marketing authorisation, the Member States shall refer to the decision adopted pursuant to paragraph 2. They shall inform the Agency accordingly.

5. Where the scope of the procedure initiated under Article 95 includes medicinal products covered by centralised marketing authorisation pursuant to Article 95(2), third subparagraph, the Commission shall, where necessary, adopt decisions to vary, suspend or revoke the marketing authorisations or to refuse the renewal of the marketing authorisations concerned in accordance with this Article.

SECTION 6

RESULTS OF EXAMINATION OF A NATIONAL MARKETING AUTHORISATION APPLICATION

Article 43

Granting of the national marketing authorisation

1. When a competent authority of the Member State grants a national marketing authorisation, it shall inform the applicant of the marketing authorisation of the summary of product characteristics, the package leaflet, the labelling as well as any conditions established in accordance with Articles 44 and 45 together with any deadlines for the fulfilment of those conditions.

2. The competent authorities of the Member States shall take all necessary measures to ensure that the information given in the summary of product characteristics is in conformity with that accepted when the national marketing authorisation is granted or subsequently.

3. The competent authorities of the Member States shall, without undue delay, make publicly available the national marketing authorisation together with the summary of product characteristics, the package leaflet as well as any conditions established in accordance with Articles 44, 45 and any obligations imposed subsequently in accordance with Article 87, together with any deadlines for the fulfilment of those conditions and obligations for each medicinal product that they have authorised.

4. The competent authority of the Member State may consider and decide upon additional evidence available, independently from the data submitted by the marketing authorisation holder. On that basis, the summary of product characteristics shall be updated if the additional evidence has an impact on the benefit-risk balance of a medicinal product.

5. The competent authorities of the Member States shall draw up an assessment report and make comments on the file as regards the results of the pharmaceutical and non-clinical tests, the clinical studies, the risk management system, the environmental risk assessment and the pharmacovigilance system of the medicinal product concerned.

6. The competent authorities of the Member States shall make the assessment report publicly available without undue delay, together with the reasons for their opinion, after deletion of any information of a commercially confidential nature. The justification shall be provided separately for each therapeutic indication applied for.

7. The public assessment report referred to in paragraph 5 shall include a summary written in a manner that is understandable to the public. The summary shall contain, in particular, a section relating to the conditions of use of the medicinal product.

Article 44

National marketing authorisation subject to conditions

1. A marketing authorisation for a medicinal product may be granted subject to one or more of the following conditions:

   (a) to take certain measures for ensuring the safe use of the medicinal product to be included in the risk management system;

   (b) to conduct post-authorisation safety studies;

   (c) to comply with obligations on the recording or reporting of suspected adverse reactions that are stricter than those referred to in Chapter IX;

   (d) any other conditions or restrictions with regard to the safe and effective use of the medicinal product;

   (e) the existence of an adequate pharmacovigilance system;

   (f) to conduct post-authorisation efficacy studies where concerns relating to some aspects of the efficacy of the medicinal product are identified and can be resolved only after the medicinal product has been marketed;

   (g) in case of medicinal products for which there is substantial uncertainty as to the surrogate endpoint relation to the expected health outcome, where appropriate and relevant for the benefit-risk balance, a post-authorisation obligation to substantiate the clinical benefit;

   (h) to conduct post-authorisation environmental risk assessment studies, collection of monitoring data or information on use, where identified or potential concerns about risks to the environment or public health, including antimicrobial resistance need to be further investigated after the medicinal product has been marketed;

   (i) to conduct post-authorisation studies to improve the safe and effective use of the medicinal product;

(j) where appropriate, to carry out medicinal product-specific validation studies to replace animal-based control methods with non-animal-based control methods.

An obligation to conduct post authorisation efficacy studies referred to in the first subparagraph, point (f), shall be based on the delegated acts adopted pursuant to Article 88.

2. The marketing authorisation shall lay down deadlines for the fulfilment of the conditions referred to in paragraph 1, first subparagraph, where necessary.

Article 45

National marketing authorisation under exceptional circumstances

1. In exceptional circumstances where, in an application under Article 6 for a marketing authorisation of a medical product, or in an application under Article 92 for a new therapeutic indication of an existing marketing authorisation, an applicant is unable to provide comprehensive data on the efficacy and safety of the medicinal product under normal conditions of use, the competent authority of the Member State may, by derogation to Article 6, grant an authorisation under Article 43, subject to specific conditions, where the following requirements are met:

(a) the applicant has demonstrated, in the application file, that there are objective and verifiable reasons not to be able to submit comprehensive data on the efficacy and safety of the medicinal product under normal conditions of use based on one of the grounds set out in Annex II;

(b) except for the data referred to in point (a), the application file is complete and satisfies all the requirements of this Directive;

(c) specific conditions are included in the decision of the competent authorities of the Member States, in particular to ensure the safety of the medicinal product as well to ensure that the marketing authorisation holder notifies to the competent authorities of the Member States any incident relating to its use and takes appropriate action where necessary.

2. The maintenance of the authorised new therapeutic indication and the validity of the national marketing authorisation shall be linked to the reassessment of the conditions set out in paragraph 1 after two years from the date when the new therapeutic indication was authorised or the marketing authorisation was granted, and thereafter at a risk-based frequency to be determined by the competent authorities of the Member State and specified in the marketing authorisation.

This reassessment shall be conducted on the basis of an application by the marketing authorisation holder to maintain the authorised new therapeutic indication or renew the marketing authorisation under exceptional circumstances.

Article 46

Validity and renewal of marketing authorisation

1. Without prejudice to paragraph 4, a marketing authorisation for a medicinal product shall be valid for an unlimited period.

By way of derogation from the first subparagraph, a national marketing authorisation granted in accordance with Article 45(1) shall be valid for five years and be subject to renewal in accordance with paragraph 2.

By way of derogation from the first subparagraph, a competent authority of the Member State may decide at the time of granting the national marketing authorisation, on objectively and duly justified grounds relating to safety of the medicinal product, to limit the validity of the national marketing authorisation to five years.

2. The marketing authorisation holder may submit an application for a renewal of a national marketing authorisation granted under paragraph 1, second or third subparagraph. Such application shall be submitted at least nine months before the national marketing authorisation ceases to be valid.

3. Once the application for a renewal has been submitted within the time limit provided for in paragraph 2, the national marketing authorisation shall remain valid until the competent authority of the Member State adopts a decision.

4. The competent authority of the Member State may renew the national marketing authorisation on the basis of a re-evaluation of the benefit-risk balance. Once renewed, the marketing authorisation shall be valid for an unlimited period.

Article 47

Refusal of a national marketing authorisation

1. The national marketing authorisation shall be refused if, after verification of the particulars and documentations referred to in Article 6 and subject to the specific requirements laid down in Articles 9 to 14, the view is taken that:

   (a) the benefit-risk balance is not considered to be favourable;

   (b) that the applicant has not properly or sufficiently demonstrated the quality, safety or efficacy of the medicinal product;

   (c) its qualitative and quantitative composition is not as declared;

   (d) the environmental risk assessment is incomplete or insufficiently substantiated by the applicant or if the risks identified in the environmental risk assessment have not been sufficiently addressed by the applicant;

   (e) the labelling and package leaflet proposed by the applicant are not in accordance with Chapter VI.

2. The national marketing authorisation shall also be refused if any particulars or documentations submitted in support of the application do not comply with Article 6, paragraphs 1 to 6, and Articles 9 to 14.

3. The applicant or the marketing authorisation holder shall be responsible for the accuracy of the particulars and documentations submitted.

SECTION 7

SPECIFIC REQUIREMENTS FOR PAEDIATRIC MEDICINAL PRODUCTS

Article 48

Compliance with the paediatric investigation plan

1. The competent authority of the Member State for which an application for marketing authorisation or variation of a marketing authorisation is submitted under the

provisions of this Chapter or of the Chapter VIII, shall verify whether it complies with the requirements laid down in Article 6(5).

2. Where the application is submitted in accordance with the procedure set out in this Chapter, Sections 3 and 4, the verification of compliance, including, as appropriate, requesting an opinion of the Agency in accordance with paragraph 3, point (b), shall be conducted by the reference Member State.

3. The Committee for Medicinal Products for Human Use, as referred to in Article 148 of [revised Regulation (EC) No 726/2004] may, in the following cases, be requested to give its opinion as to whether studies conducted by the applicant are in compliance with the agreed paediatric investigation plan as defined in Article 74 of [revised Regulation (EC) No 726/2004]:

   (a) by the applicant, prior to submitting an application for a marketing authorisation or for a variation of a marketing authorisation;

   (b) by the competent authority of the Member State, when validating an application for a marketing authorisation or for a variation of a marketing authorisation that does not already include such an opinion.

4. In the case of a request in accordance with paragraph 3, point (a), the applicant shall not submit its application until the Committee for Medicinal Products for Human Use has provided its opinion, and a copy thereof shall be annexed to the application.

5. Member States shall take due account of an opinion drawn up in accordance with paragraph 3.

6. When the competent authority of the Member State, during the scientific assessment of a valid application for a marketing authorisation or a variation of a marketing authorisation, concludes that the studies are not in conformity with the agreed paediatric investigation plan, the medicinal product shall not be eligible for the rewards and incentives provided for in Article 86.

Article 49

Data deriving from a paediatric investigation plan

1. Where a marketing authorisation or a variation of a marketing authorisation, is granted in accordance with the provisions under this Chapter or of the provisions under Chapter VIII:

   (a) the results of all clinical studies, conducted in compliance with an agreed paediatric investigation plan as referred to in Article 6(5), point (a), shall be included in the summary of product characteristics and, if appropriate, in the package leaflet, or

   (b) any agreed waiver as referred to in Article 6(5), points (b) and (c), shall be recorded in the summary of product characteristics and, if appropriate, in the package leaflet of the medicinal product concerned.

2. If the application complies with all the measures contained in the agreed completed paediatric investigation plan and if the summary of product characteristics reflects the results of studies conducted in compliance with that agreed paediatric investigation plan, the competent authority of the Member State shall include within the marketing authorisation a statement indicating compliance of the application with the agreed completed paediatric investigation plan.

3. An application for new therapeutic indications, including paediatric indications, new pharmaceutical forms, new strengths and new routes of administration of medicinal products authorised in accordance with the provisions under this Chapter or of the provisions under Chapter VIII and which are protected either by a supplementary protection certificate under [Regulation (EC) No 469/2009 - OP please replace reference by new instrument when adopted], or by a patent which qualifies for the granting of the supplementary protection certificate, may be submitted under the procedure laid down in Articles 41 and 42.

4. The procedure referred to in paragraph 3 shall be limited to the assessment of the specific section of the summary of product characteristics to be varied.

Chapter IV
Prescription status

Article 50

Prescription status of medicinal products

1. When a marketing authorisation is granted, the competent authorities shall, by applying the criteria laid down in Article 51, specify the prescription status of the medicinal product as:

   (a) a medicinal product subject to medical prescription; or

   (b) a medicinal product not subject to medical prescription.

2. The competent authorities may fix sub-categories for medicinal products that are subject to medical prescription. In that case, they shall specify the following prescription status:

   (a) medicinal products subject to medical prescription for renewable or non-renewable delivery;

   (b) medicinal products subject to special medical prescription;

   (c) medicinal products on ‘restricted’ medical prescription, reserved for use in certain specialised areas.

Article 51

Medicinal products subject to medical prescription

1. A medicinal product shall be subject to medical prescription where it:

   (a) is likely to present a danger either directly or indirectly, even when used correctly, if used without medical supervision;

   (b) is frequently and to a very wide extent used incorrectly, and as a result is likely to present a direct or indirect danger to human health;

   (c) contains substances or preparations thereof, the activity or adverse reactions of which require further investigation;

   (d) is normally prescribed by a doctor to be administered parenterally;

   (e) is an antimicrobial; or

(f) contains an active substance which are persistent, bioaccumulative and toxic, or very persistent and very bioaccumulative, or persistent, mobile and toxic, or very persistent and very mobile for which medical prescription is required as risk minimisation measure with regard to the environment, unless the use of the medicinal product and the patient safety require otherwise.

2. Member States may set additional conditions on the prescription of antimicrobials, restrict the validity of medical prescription and limit the quantities prescribed to the amount required for the treatment or therapy concerned or submitting certain antimicrobial medicinal products to special medical prescription or restricted prescription.

3. Where Member States provide for the sub-category of medicinal products subject to special medical prescription, they shall take account of the following factors:

(a) the medicinal product contains, in a non-exempt quantity, a substance classified as a narcotic or a psychotropic substance within the meaning of the international conventions;

(b) the medicinal product is likely, if incorrectly used, to present a substantial risk of medicinal abuse, to lead to addiction or be misused for illegal purposes; or

(c) the medicinal product contains a substance that, by reason of its novelty or properties, could be considered as belonging to the group set out in point (a) as a precautionary measure.

4. Where Member States provide for the sub-category of medicinal products subject to restricted prescription, they shall take account of the following factors:

(a) the medicinal product, because of its pharmaceutical characteristics or novelty or in the interests of public health, is reserved for treatments that can only be followed in a hospital environment;

(b) the medicinal product is used in the treatment of conditions that must be diagnosed in a hospital environment or in institutions with adequate diagnostic facilities, although administration and follow-up may be carried out elsewhere;

(c) the medicinal product is intended for outpatients but its use may produce very serious adverse reactions requiring a prescription drawn up as required by a specialist and special supervision throughout the treatment.

5. A competent authority may waive application of the paragraphs 1, 3 and 4 having regard to:

(a) the maximum single dose, the maximum daily dose, the strength, the pharmaceutical form, certain types of packaging; or

(b) other circumstances of use that it has specified.

6. If a competent authority does not designate medicinal products into sub-categories referred to in Article 50(2), it shall nevertheless take into account the criteria laid down in paragraphs 3 and 4 in determining whether any medicinal product shall be classified as a medicinal product subject to medical prescription.

Article 52

Medicinal products not subject to medical prescription

Medicinal products not subject to medical prescription shall be those that do not meet the criteria laid down in Article 51.

Article 53

List of medicinal products subject to medical prescription

The competent authorities shall draw up a list of the medicinal products subject, on their territory, to medical prescription, specifying, if necessary, the category of prescription status. They shall update this list annually.

Article 54

Amendment of prescription status

When new facts are brought to their attention, the competent authorities shall examine and, as appropriate, amend the prescription status of a medicinal product by applying the criteria listed in Article 51.

Article 55

Data protection of evidence for the change of prescription status

Where a change of prescription status of a medicinal product has been authorised on the basis of significant non-clinical tests or clinical studies, the competent authority shall not refer to the results of those tests or studies when examining an application by another applicant for or marketing authorisation holder for a change of prescription status of the same substance for one year after the initial change was authorised.

Chapter V
Obligations and liability of the marketing authorisation holder

Article 56

General obligations

1. The marketing authorisation holder shall be responsible for the making available on the market of the medicinal product covered by the marketing authorisation it has been granted. The designation of a marketing authorisation holder representative shall not relieve the marketing authorisation holder of its legal responsibility.

2. The marketing authorisation holder of a medicinal product placed on the market in a Member State shall notify the competent authority of the Member State concerned of the date of actual placing on the market of the medicinal product in that Member State, taking into account the various presentations authorised.

3. The marketing authorisation holder of a medicinal product placed on the market in a Member State shall, within the limits of its responsibility, ensure appropriate and continued supplies of that medicinal product to wholesale distributors, pharmacies or persons authorised to supply medicinal products so that the needs of patients in the Member State in question are covered.

   The arrangements for implementing the first subparagraph should, moreover, be justified on grounds of public health protection and be proportionate in relation to the

objective of such protection, in compliance with the Treaty rules, particularly those concerning the free movement of goods and competition.

4. The marketing authorisation holder shall, at all stages of manufacturing and distribution ensure that the starting materials and ingredients of the medicinal products and the medicinal products themselves comply with the requirements of this Directive and, where relevant, the [revised Regulation (EC) No 726/2004] and other Union law and shall verify that such requirements are met.

5. For integral combination of a medicinal product with a medical device and for combinations of a medicinal product with a product other than a medical device, the marketing authorisation holder shall be responsible for the whole product in terms of compliance of the medicinal product with the requirements of this Directive and the [revised Regulation (EC) No 726/2004].

6. The marketing authorisation holder shall be established in the Union.

7. Where the marketing authorisation holder considers or has reason to believe that the medicinal product it has made available on the market is not in conformity with the marketing authorisation or this Directive and the [revised Regulation (EC) No 726/2004] it shall immediately take the necessary corrective actions to bring that medicinal product into conformity, to withdraw it or recall it, as appropriate. The marketing authorisation holder shall immediately inform the competent authorities and the distributors concerned to that effect.

8. Upon request, the marketing authorisation holder shall provide the competent authorities with free samples in sufficient quantities to enable controls to be made on the medicinal products that it has placed on the market.

9. Upon request the marketing authorisation holder shall provide the competent authority with all data relating to the volume of sales of the medicinal product, and any data in its possession relating to the volume of prescriptions.

Article 57

Responsibility to report on public financial support

1. The marketing authorisation holder shall declare to the public any direct financial support received from any public authority or publicly funded body, in relation to any activities for the research and development of the medicinal product covered by a national or a centralised marketing authorisation, irrespective of the legal entity that received that support.

2. Within 30 days after the marketing authorisation is granted the marketing authorisation holder shall:

   (a) draw up an electronic report listing:

      (i) the amount of financial support received and the date thereof;

      (ii) the public authority or publicly funded body that provided the financial support referred to in point (i);

      (iii) the legal entity that received the support referred to in point (i).

   (b) ensure that the electronic report is accurate and that it has been audited by an independent external auditor;

   (c) make the electronic report accessible to the public via a dedicated webpage;

(d) communicate the electronic link to such webpage to the competent authority of the Member State or, where appropriate, to the Agency.

3. For the medicinal products authorised under this Directive, the competent authority of the Member State shall communicate in a timely manner the electronic link to the Agency.

4. The marketing authorisation holder shall keep the electronic link up to date and, as necessary, update the report annually.

5. The Member States shall take appropriate measures to ensure that paragraphs 1, 2 and 4 are complied with by the marketing authorisation holder established in their country.

6. The Commission may adopt implementing acts to lay down the principles and format for the information to be reported pursuant to paragraph 2. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 214(2).

Article 58

Traceability of substances used in the manufacture of medicinal products

1. The marketing authorisation holder shall, when necessary, ensure the traceability of an active substance, starting material, excipient or any other substance intended or expected to be present in a medicinal product at all stages of manufacturing and distribution.

2. The marketing authorisation holder shall be able to identify any natural or legal person from whom they have been supplied with an active substance, starting material, excipient or any other substance intended or expected to be present in a medicinal product.

3. The marketing authorisation holder and its suppliers of an active substance, starting material, excipient or any other substance used in the manufacturing of a medicinal product shall have in place systems and procedures that allow for the information referred to in paragraph 2 to be made available, upon request, to the competent authorities.

4. The marketing authorisation holder and its suppliers shall have in place systems and procedures to identify the other natural or legal persons to whom products referred to in paragraph 2 have been supplied. This information shall, upon request, be made available to the competent authorities.

Article 59

Placing on the market of products with paediatric indications

Where medicinal products are authorised for a paediatric indication following completion of an agreed paediatric investigation plan and those medicinal products have already been marketed with other therapeutic indications, the marketing authorisation holder shall, within two years of the date on which the paediatric indication is authorised, place the medicinal product on the market taking into account the paediatric indication in all Member States where the medicinal product is already placed on the market.

A register, coordinated by the Agency, and made publicly available, shall mention these deadlines.

Article 60

Discontinuation of the placing on the market of paediatric products

If a medicinal product is authorised for a paediatric indication and the marketing authorisation holder has benefited from rewards or incentives under Article 86 of this Directive or Article 93 of [revised Regulation (EC) No 726/2004], and these periods of protection have expired, and if the marketing authorisation holder intends to discontinue placing the medicinal product on the market, the marketing authorisation holder shall transfer the marketing authorisation to a third party or allow a third party, which has declared its intention to continue to place the medicinal product in question on the market, to use the pharmaceutical, non-clinical and clinical documentation contained in the file of the medicinal product on the basis of Article 14.

The marketing authorisation holder shall inform the competent authorities of its intention to discontinue the placing on the market of the medicinal product no less than twelve months before the discontinuation. The competent authorities shall make this fact publicly available.

Article 61

Liability of the marketing authorisation holder

The marketing authorisation shall not affect the civil and criminal liability of the marketing authorisation holder.

Chapter VI
Product information and labelling

Article 62

Summary of product characteristics

1. The summary of product characteristics shall contain the particulars listed in Annex V.

2. For marketing authorisations under Articles 9 and 11 and subsequent variations to such marketing authorisations, if one or more of the therapeutic indications, posologies, pharmaceutical forms, methods or routes of administration or any other way in which the medicinal product may be used are still covered by patent law or a supplementary protection certificate for medicinal products at the time when the generic or biosimilar medicinal product was marketed, the applicant for an authorisation for a generic or biosimilar medicinal product may request not to include this information in their marketing authorisation.

3. For all medicinal products, a standard text shall be included in the summary of product characteristics expressly asking healthcare professionals to report any suspected adverse reaction in accordance with the national reporting system referred to in Article 106(1). Different ways of reporting, including electronic reporting, shall be available in compliance with Article 106(1), second subparagraph.

Article 63

General principles on package leaflet

1. A package leaflet shall be mandatory for medicinal products.

2. The package leaflet shall be written and designed in a clear and understandable way, enabling users to act appropriately, when necessary with the help of healthcare professionals.

3. Member States may decide that the package leaflet shall be made available in paper format or electronically, or both. In the absence of such specific rules in a Member State, a package leaflet in paper format shall be included in the packaging of a medicinal product. If the package leaflet is only made available electronically, the patient's right to a printed copy of the package leaflet should be guaranteed upon request and free of charge and it should be ensured that the information in digital format is easily accessible to all patients.

4. By derogation from paragraphs 1 and 2, where the information required under Articles 64 and 73 is directly conveyed on the outer packaging or on the immediate packaging, a package leaflet shall not be required.

5. The Commission is empowered to adopt delegated acts in accordance with Article 215 to amend paragraph 3 by making mandatory the electronic version of the package leaflet. That delegated act shall also establish the patient's right to a printed copy of the package leaflet upon request and free of charge. The delegation of powers shall apply as of [OP please insert the date = five years following 18 months after the date of entering into force of this Directive].

6. The Commission shall adopt implementing acts in accordance with the examination procedure referred to in Article 214(2) to establish common standards for the electronic version of the package leaflet, the summary of product characteristics and the labelling, taking into account available technologies.

7. Where the package leaflet is made available electronically, the individual right to privacy shall be ensured. Any technology giving access to the information shall not allow the identification or tracking of individuals, nor shall it be used for commercial purposes.

Article 64

Content of package leaflet

1. The package leaflet shall be drawn up in accordance with the summary of product characteristics, referred to in Article 62(1) and shall include the particulars listed in Annex VI.

2. For all medicinal products, a standardised text shall be included, expressly asking patients to communicate any suspected adverse reaction to their doctor, pharmacist, healthcare professional or directly to the national reporting system referred to in Article 106(1), and specifying the different ways of reporting available (electronic reporting, postal address or others) in compliance with Article 106(1), second subparagraph.

3. The package leaflet shall reflect the results of consultations with target patient groups to ensure that it is legible, clear and easy to use.

Article 65

Content of labelling particulars

1. The outer packaging of medicinal products or, where there is no outer packaging, the immediate packaging, with the exception of the packaging referred to in Article 66, paragraphs 2 and 3, shall include the labelling particulars listed in Annex IV.

2. The Commission is empowered to adopt delegated acts in accordance with Article 215 to:

   (a) amend the list of labelling particulars set out in Annex IV in order to take account of scientific progress or patient needs;

   (b) supplement Annex IV by setting out a reduced list of mandatory labelling particulars that shall appear on the outer packaging of multi-language packages.

Article 66

Labelling of blister packs or small immediate packaging

1. The particulars laid down in Annex IV shall appear on immediate packagings other than those referred to in the paragraphs 2 and 3.

2. The following particulars at least shall appear on immediate packagings that take the form of blister packs and are placed in an outer packaging that complies with the requirements laid down in Articles 65 and 73.

   (a) the name of the medicinal product;

   (b) the name of the marketing authorisation holder placing the product on the market;

   (c) the expiry date;

   (d) the batch number.

3. The following particulars at least shall appear on small immediate packaging units on which the particulars laid down in Articles 65 and 73 cannot be displayed, shall include at least the following labelling particulars:

   (a) the name of the medicinal product and, if necessary, the route of administration;

   (b) the method of administration;

   (c) the expiry date;

   (d) the batch number;

   (e) the contents by weight, by volume or by unit.

Article 67

Safety features

1. Medicinal products subject to prescription shall bear the safety features referred to in Annex IV, unless they have been listed in accordance with the procedure referred to in paragraph 2, second subparagraph, point (b).

   Medicinal products not subject to prescription shall not bear the safety features referred to in Annex IV, unless, by way of exception, they have been listed in accordance with the procedure referred to in paragraph 2, second subparagraph, point (b).

2. The Commission shall adopt delegated acts in accordance with Article 215 to supplement Annex IV by laying down detailed rules for the safety features.

Those delegated acts shall set out:

(a) the characteristics and technical specifications of the unique identifier of the safety features referred to in Annex IV that enables the authenticity of medicinal products to be verified and individual packs to be identified;

(b) the lists containing the medicinal products or product categories that, in the case of medicinal products subject to prescription shall not bear the safety features, and in the case of medicinal products not subject to prescription shall bear the safety features referred to in Annex IV;

(c) the procedures for the notification to the Commission provided for in paragraph 4 and a rapid system for evaluating and deciding on such notification for the purpose of applying point (b);

(d) the modalities for the verification of the safety features referred to in Annex IV by the manufacturers, wholesale distributors, pharmacists and natural or legal persons authorised or entitled to supply medicinal products to the public and by the competent authorities;

(e) provisions on the establishment, management and accessibility of the repositories system in which information on the safety features, enabling the verification of the authenticity and identification of medicinal products, as provided for in Annex IV, shall be contained.

The lists referred to in the second subparagraph, point (b), shall be established considering the risk of falsification relating to the medicinal products or categories of medicinal products concerned. To this end, at least the following criteria shall be applied:

(a) the price and sales volume of the medicinal product;

(b) the number and frequency of previous cases of falsified medicinal products being reported within the Union and in third countries and the evolution of the number and frequency of such cases to date;

(c) the specific characteristics of the medicinal products concerned;

(d) the severity of the conditions intended to be treated;

(e) other potential risks to public health.

The modalities referred to in the second subparagraph, point (d), shall allow the verification of the authenticity of each supplied pack of the medicinal products bearing the safety features referred to in Annex IV and determine the extent of such verification. When establishing those modalities, the particular characteristics of the supply chains in Member States, and the need to ensure that the impact of verification measures on particular actors in the supply chains is proportionate, shall be taken into account.

For the purposes of the second subparagraph, point (e), the costs of the repositories system shall be borne by the manufacturing authorisation holders of medicinal products bearing the safety features.

3. When adopting delegated acts referred to in paragraph 2, the Commission shall take due account of at least the following:

(a) the protection of personal data as provided for in Union law;

(b) the legitimate interests to protect information of a commercially confidential nature;

(c) the ownership and confidentiality of the data generated by the use of the safety features; and

(d) the cost-effectiveness of the measures.

4. The competent authorities of the Member States shall notify the Commission of non-prescription medicinal products that they judge to be at risk of falsification and may inform the Commission of medicinal products that they deem not to be at risk of falsification in accordance with the criteria set out in paragraph 2, second subparagraph, point (b).

5. Member States may, for the purposes of reimbursement or pharmacovigilance, extend the scope of application of the unique identifier referred to in Annex IV to any medicinal product subject to prescription or subject to reimbursement.

6. Member States may, for the purposes of reimbursement, pharmacovigilance, pharmacoepidemiology or for data protection prolongation for market launch use the information contained in the repositories system referred to paragraph 2, second subparagraph, point (e).

7. Member States may, for the purposes of patient safety, extend the scope of application of the anti-tampering device referred to in Annex IV to any medicinal product.

Article 68

Labelling and instruction leaflet of radionuclides and radiopharmaceuticals

1. In addition to the rules laid down in this Chapter, the outer carton and the container of medicinal products containing radionuclides shall be labelled in accordance with the regulations for the safe transport of radioactive materials laid down by the International Atomic Energy Agency. Moreover, the labelling shall comply with the provisions set out in paragraphs 2 and 3.

2. The label on the shielding shall include the particulars laid down in Article 65. In addition, the label on the shielding shall explain in full, the codings used on the vial and shall indicate, where necessary, for a given time and date, the amount of radioactivity per dose or per vial and the number of capsules, or, for liquids, the number of millilitres in the container.

3. The vial shall be labelled with the following information:

(a) the name or code of the medicinal product, including the name or chemical symbol of the radionuclide;

(b) the batch identification and expiry date;

(c) the international symbol for radioactivity;

(d) the name and address of the manufacturer;

(e) the amount of radioactivity as specified in paragraph 2.

4. The competent authority shall ensure that a detailed instruction leaflet is enclosed with the packaging of radiopharmaceuticals, radionuclide generators, radionuclide

kits or radionuclide precursors. The text of this leaflet shall be established in accordance with Article 64(1). In addition, the leaflet shall include any precautions to be taken by the user and the patient during the preparation and administration of the medicinal product and special precautions for the disposal of the packaging and its unused contents.

Article 69

Special information requirements for antimicrobials

1. The marketing authorisation holder shall ensure availability of educational material to healthcare professionals, including through medical sales representatives as referred to in Article 175(1), point (c), regarding the appropriate use of diagnostic tools, testing or other diagnostic approaches related to antimicrobial-resistant pathogens, that may inform on the use of the antimicrobial.

2. The marketing authorisation holder shall include in the packaging of antimicrobials a document that contains specific information about the medicinal product concerned and that is made available to the patient in addition to the product leaflet (“awareness card”) with information on antimicrobial resistance and the appropriate use and disposal of antimicrobials.

   Member States may decide that the awareness card shall be made available in paper format or electronically, or both. In the absence of such specific rules in a Member State, an awareness card in paper format shall be included in the packaging of an antimicrobial.

3. The text of the awareness card shall be aligned with Annex VI.

Article 70

Legibility

The package leaflet and labelling particulars referred to in this Chapter shall be easily legible, clearly comprehensible and indelible.

Article 71

Accessibility for persons with disabilities

The name of the medicinal product shall also be expressed in Braille format on the packaging. The marketing authorisation holder shall ensure that the package leaflet referred to in Article 63 is made available upon request from patients' organisations in formats appropriate for persons with disabilities, including blind and partially-sighted persons.

Article 72

Member States labelling requirements

1. Notwithstanding Article 77 Member States may require the use of certain forms of labelling of the medicinal product making it possible to ascertain:

   (a) the price of the medicinal product;

   (b) the reimbursement conditions of social security organisations;

   (c) the legal status for supply to the patient, in accordance with Chapter IV;

(d) authenticity and identification in accordance with Article 67(5).

2. For medicinal products for which a centralised marketing authorisation as referred to in Article 5 has been granted, Member States shall, when applying this Article, observe the detailed guidance referred to in Article 77.

Article 73

Symbols and pictogram

The outer packaging and the package leaflet may include symbols or pictograms designed to clarify certain information set out in Articles 64(1) and 65 and other information compatible with the summary of product characteristics that is useful for the patient, to the exclusion of any element of a promotional nature.

Article 74

Requirements on languages

1. The particulars for labelling listed in Articles 64 and 65, shall appear in an official language or official languages of the Member State where the medicinal product is placed on the market, as specified, for the purposes of this Directive, by that Member State.

2. Paragraph 1 shall not prevent those particulars from being indicated in several languages, provided that the same particulars appear in all the languages used.

3. The package leaflet must be clearly legible in an official language or official languages of the Member State where the medicinal product is placed on the market, as specified, for the purposes of this Directive, by that Member State.

4. The competent authorities of the Member State may also grant a full or partial exemption to the obligation that the labelling and the package leaflet must be in an official language or official languages of the Member State where the medicinal product is placed on the market, as specified, for the purposes of this Directive, by that Member State. For the purpose of multi-language packages, Member States may allow the use on the labelling and package leaflet of an official language of the Union that is commonly understood in the Member States where the multi-language package is marketed.

Article 75

Member States exemptions from requirements for labelling and package leaflet

The competent authorities of the Member States may, subject to measures they consider necessary to safeguard public health, grant an exemption to the obligation that the particulars required in Articles 64 and 65 should appear on the labelling and in the package leaflet in the following cases:

(a) where the medicinal product is not intended to be delivered directly to the patient;

(b) where there are problems in respect of the availability of the medicinal product;

(c) where there are space constraints due to the size of the packaging or of the package leaflet or in case of multilingual packages or package leaflets;

(d) in the context of a public health emergency;

(e) to facilitate access to medicines in Member States.

Article 76

Approval of the labelling and package leaflet information

1. One or more mock-ups of the outer packaging and the immediate packaging of a medicinal product, together with the package leaflet, shall be submitted to the competent authorities for authorising marketing when the marketing authorisation is requested. The results of assessments carried out in cooperation with target patient groups shall also be provided to the competent authority.

2. The competent authority shall refuse the marketing authorisation if the labelling or the package leaflet do not comply with the provisions of this Chapter or if they are not in accordance with the particulars listed in the summary of product characteristics.

3. All proposed changes to an aspect of the labelling or the package leaflet covered by this Chapter and not connected with the summary of product characteristics shall be submitted to the competent authorities. If the competent authorities have not opposed a proposed change within 90 days following the introduction of the request, the applicant may put the change into effect.

4. The fact that the competent authority does not refuse a marketing authorisation pursuant to paragraph 2 or a change to the labelling or the package leaflet pursuant to paragraph 3 does not alter the general legal liability of the manufacturer and the marketing authorisation holder.

Article 77

Guidance on labelling particulars

In consultation with the Member States and the parties concerned, the Commission shall draw up and publish detailed guidance concerning in particular:

(a) the wording of certain special warnings for certain categories of medicinal products;

(b) the particular information needs relating to non-prescription medicinal products;

(c) the legibility of particulars on the labelling and package leaflet;

(d) the methods for the identification and authentication of medicinal products;

(e) the list of excipients that must feature on the labelling of medicinal products and the way in which these excipients must be indicated;

(f) harmonised provisions for the implementation of Article 72.

Article 78

Placing on the market of labelled medicinal products

Member States may not prohibit or impede the placing on the market of medicinal products within their territory on grounds connected with labelling or the package leaflet where these comply with the requirements of this Chapter.

Article 79

Non-compliance with the requirements for labelling and package leaflet

Where the provisions of this Chapter are not complied with, and a notice served on the marketing authorisation holder concerned has remained without effect, the competent authorities of the Member States may suspend the marketing authorisation, until the labelling and the package leaflet of the medicinal product in question have been made to comply with the requirements of this Chapter.

Chapter VII
Regulatory protection, unmet medical needs and rewards for paediatric medicinal products

Article 80

Regulatory data and market protection

1. The data referred to in Annex I, originally submitted with the view to obtaining a marketing authorisation shall not be referred to by another applicant for a subsequent marketing authorisation during the period determined in accordance with Article 81 ('regulatory data protection period').

2. A medicinal product concerned by a subsequent marketing authorisation referred to in paragraph 1 shall not be placed on the market for a period of two years after the expiry of the relevant regulatory data protection periods referred to in Article 81.

3. By way of derogation from paragraph 1, the marketing authorisation holder concerned may grant the marketing authorisation applicant for another marketing authorisation a letter of access to its data submitted under Annex I, as referred to in Article 14.

4. By way of derogation from the paragraphs 1 and 2, when a compulsory licence has been granted by a relevant authority in the Union to a party to address a public health emergency, the data and market protection shall be suspended with regard to that party insofar as the compulsory licence requires, and during the duration period of the compulsory licence.

5. The data protection period set out to in paragraph 1 shall also apply in Member States where the medicinal product is not authorised or is no longer authorised.

Article 81

Regulatory data protection periods

1. The regulatory data protection period shall be six years from the date when the marketing authorisation for that medicinal product was granted in accordance with Article 6(2). For marketing authorisations that belong to the same global marketing authorisation the period of data protection shall start from the date when the initial marketing authorisation was granted in the Union.

2. Subject to a scientific evaluation by the relevant competent authority, the data protection period referred to in paragraph 1 shall be prolonged by:

   (a) 24 months, where the marketing authorisation holder demonstrates that the conditions referred to in Article 82(1) are fulfilled within two years, from the

date when the marketing authorisation was granted or, within three years from that date for any of the following entities:

(i) SMEs within the meaning of Commission Recommendation 2003/361/EC;

(ii) entities not engaged in an economic activity ('not-for-profit entity'); and

(iii) undertakings that, by the time of granting of a marketing authorisation, have received not more than five centralised marketing authorisations for the undertaking concerned or, in the case of an undertaking belonging to a group, for the group of which it is part, since the establishment of the undertaking or the group, whichever is earliest.

(b) six months, where the marketing authorisation applicant demonstrates at the time of the initial marketing authorisation application that the medicinal product addresses an unmet medical need as referred to in Article 83;

(c) six months, for medicinal products containing a new active substance, where the clinical trials supporting the initial marketing authorisation application use a relevant and evidence-based comparator in accordance with scientific advice provided by the Agency;

(d) 12 months, where the marketing authorisation holder obtains, during the data protection period, an authorisation for an additional therapeutic indication for which the marketing authorisation holder has demonstrated, with supporting data, a significant clinical benefit in comparison with existing therapies.

In the case of a conditional marketing authorisation granted in accordance with Article 19 of [revised Regulation (EC) No 726/2004] the prolongation referred to in the first subparagraph, point (b), shall only apply if, within four years of the granting of the conditional marketing authorisation, the medicinal product has been granted a marketing authorisation in accordance with Article 19(7) of [revised Regulation (EC) No 726/2004.

The prolongation referred to in the first subparagraph, point (d), may only be granted once.

3. The Agency shall set the scientific guidelines referred to in paragraph 2, point (c), on criteria for proposing a comparator for a clinical trial, taking into account the results of the consultation of the Commission and the authorities or bodies involved in the mechanism of consultation referred to in Article 162 of [revised Regulation (EC) No 726/2004].

Article 82

Prolongation of the data protection period for medicinal products supplied in Member States

1. The prolongation of the data protection period referred to in Article 81(2), first subparagraph, point (a), shall only be granted to medicinal products if they are released and continuously supplied into the supply chain in a sufficient quantity and in the presentations necessary to cover the needs of the patients in the Member States in which the marketing authorisation is valid.

The prolongation referred to in the first subparagraph shall apply to medicinal products that have been granted a centralised marketing authorisation, as referred to

in Article 5 or that have been granted a national marketing authorisation through the decentralised procedure, as referred to in Chapter III, Section 3.

2. To receive a prolongation referred to in Article 81(2), first subparagraph, point (a), the marketing authorisation holder shall apply for a variation of the relevant marketing authorisation.

The application for a variation shall be submitted between 34 and 36 months after the date when the initial marketing authorisation was granted, or for entities referred to in Article 81(2), first subparagraph, point (a), between 46 and 48 months, after that date.

The application for a variation shall contain documentation from the Member States in which the marketing authorisation is valid. Such documentation shall:

(a) confirm that the conditions set out in paragraph 1 have been satisfied in their territory; or

(b) waive the conditions set out in paragraph 1 in their territory for the purpose of the prolongation.

Positive decisions adopted in accordance with Articles 2 and 6 of Council Directive 89/105/EEC[37] shall be considered equivalent to a confirmation referred to in the third subparagraph, point (a).

3. To receive the documentation referred to in paragraph 2, third subparagraph, the marketing authorisation holder shall make a request to the relevant Member State. Within 60 days from the request of the marketing authorisation holder, the Member State shall issue a confirmation of compliance or, a reasoned statement of non-compliance or alternatively provide a statement of non-objection to prolong the period of regulatory data protection pursuant to this Article.

4. In cases where a Member State has not replied to the application of the marketing authorisation holder within the deadline referred to in paragraph 3, it shall be considered that a statement of non-objection has been provided.

For medicinal products granted a centralised marketing authorisation the Commission shall vary the marketing authorisation pursuant to Article 47 of [revised Regulation (EC) No 726/2004] to prolong the data protection period. For medicinal products granted a marketing authorisation in accordance with the decentralised procedure, the competent authorities of the Member States shall vary the marketing authorisation pursuant to Article 92 to prolong the data protection period**.**

5. Member States representatives may request the Commission to discuss issues related to the practical application of this Article in the Committee established by Council Decision 75/320/EEC[38] ('Pharmaceutical Committee'). The Commission may invite bodies responsible for health technology assessment as referred to in Regulation (EU) 2021/2282 or national bodies responsible for pricing and reimbursement, as required, to participate in the deliberations of the Pharmaceutical Committee.

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37 Council Directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of national health insurance systems (OJ L 40, 11.2.1989, p. 8).

38 Council Decision of 20 May 1975 setting up a pharmaceutical committee (OJ L 147, 9.6.1975, p. 23).

6. The Commission, based on the experience of Member States and relevant stakeholders, may adopt implementing measures relating to the procedural aspects outlined in this Article and regarding the conditions mentioned in paragraph 1. Those implementing acts shall be adopted in accordance with the procedure referred to in Article 214(2).

Article 83

Medicinal products addressing an unmet medical need

1. A medicinal product shall be considered as addressing an unmet medical need if at least one of its therapeutic indications relates to a life threatening or severely debilitating disease and the following conditions are met:

   (a) there is no medicinal product authorised in the Union for such disease, or, where despite medicinal products being authorised for such disease in the Union, the disease is associated with a remaining high morbidity or mortality;

   (b) the use of the medicinal product results in a meaningful reduction in disease morbidity or mortality for the relevant patient population.

2. Designated orphan medicinal products referred to in Article 67 of [revised Regulation (EC) No 726/2004] shall be considered as addressing an unmet medical need.

3. Where the Agency adopts scientific guidelines for the application of this Article it shall consult the Commission and the authorities or bodies referred to in Article 162 of [revised Regulation (EC) No 726/2004].

Article 84

Data protection for repurposed medicinal products

1. A regulatory data protection period of four years shall be granted for a medicinal product with respect to a new therapeutic indication not previously authorised in the Union, provided that:

   (a) adequate non-clinical or clinical studies were carried out in relation to the therapeutic indication demonstrating that it is of significant clinical benefit, and

   (b) the medicinal product is authorised in accordance with Articles 9 to 12 and has not previously benefitted from data protection, or 25 years have passed since the granting of the initial marketing authorisation of the medicinal product concerned.

2. The data protection period referred to in paragraph 1 may only be granted once for any given medicinal product.

3. During the data protection period referred to in paragraph 1, the marketing authorisation shall indicate that the medicinal product is an existing medicinal product authorised in the Union that has been authorised with an additional therapeutic indication.

Article 85

Exemption to the protection of intellectual property rights

Patent rights, or supplementary protection certificates under the [Regulation (EC) No 469/2009 - OP please replace reference by new instrument when adopted] shall not be regarded as infringed when a reference medicinal product is used for the purposes of:

(a) studies, trials and other activities conducted to generate data for an application, for:

(i) a marketing authorisation of generic, biosimilar, hybrid or bio-hybrid medicinal products and for subsequent variations;

(ii) health technology assessment as defined in Regulation (EU) 2021/2282;

(iii) pricing and reimbursement.

(b) the activities conducted exclusively for the purposes set out in point (a), may cover the submission of the application for a marketing authorisation and the offer, manufacture, sale, supply, storage, import, use and purchase of patented medicinal products or processes, including by third party suppliers and service providers.

This exception shall not cover the placing on the market of the medicinal products resulting from such activities.

Article 86

Rewards for paediatric medicinal products

1. Where an application for marketing authorisation, includes the results of all studies conducted in compliance with an agreed paediatric investigation plan, the holder of the patent or supplementary protection certificate shall be entitled to a six-month extension of the period referred to in Article 13, paragraphs 1 and 2 of [Regulation (EC) No 469/2009 - OP please replace reference by new instrument when adopted].

The first subparagraph shall also apply where completion of the agreed paediatric investigation plan fails to lead to the authorisation of a paediatric indication, but the results of the studies conducted are reflected in the summary of product characteristics and, if appropriate, in the package leaflet of the medicinal product concerned.

2. The inclusion in a marketing authorisation of the statement referred to in Article 49(2) of this Directive or in Article 90(2) of [revised Regulation (EC) No 726/2004] shall be used for the purposes of applying paragraph 1.

3. Where the procedures laid down in Chapter III, Sections 3 and 4, have been used, the six-month extension of the period referred to in paragraph 1 shall be granted only if the product is authorised in all Member States.

4. In the case of an application for new therapeutic indications, including paediatric indications, new pharmaceutical forms, new strengths and new routes of administration of authorised medicinal products which are protected either by a supplementary protection certificate under [Regulation (EC) No 469/2009 - OP please replace reference by new instrument when adopted], or by a patent which qualifies for the granting of the supplementary protection certificate which leads to the authorisation of a new paediatric indication, paragraphs 1, 2 and 3 shall not apply if the applicant applies for, and obtains, a one-year extension of the period of marketing protection for the medicinal product concerned, on the grounds that this new paediatric indication brings a significant clinical benefit in comparison with existing therapies, in accordance with Article 81(2), first subparagraph, point (d).

Chapter VIII
Post-marketing authorisation measures

Article 87

Imposed post-authorisation studies

1. After the granting of a marketing authorisation, the competent authority of the Member State may impose an obligation on the marketing authorisation holder:

   (a) to conduct a post-authorisation safety study if there are concerns about the risks of an authorised medicinal product. If the same concerns apply to more than one medicinal product, the competent authority of the Member State shall, following consultation with the Pharmacovigilance Risk Assessment Committee, encourage the marketing authorisation holders concerned to conduct a joint post-authorisation safety study;

   (b) to conduct a post-authorisation efficacy study when the understanding of the disease or the clinical methodology indicate that previous efficacy evaluations might have to be revised significantly. The obligation to conduct the post-authorisation efficacy study shall be based on the delegated acts adopted pursuant to Article 88 while taking into account the scientific guidance referred to in Article 123.

   (c) to conduct a post-authorisation environmental risk assessment study, collection of monitoring data or information on use, if there are concerns about the risks to the environment or public health, including antimicrobial resistance, due to an authorised medicinal product, or related active substance.

   If the same concerns apply to more than one medicinal product, the competent authority of Member State shall, following consultation with the Agency, encourage the marketing authorisation holders concerned to conduct a joint post-authorisation environmental risk assessment study.

   The imposition of such an obligation shall be duly justified, notified in writing, and shall include the objectives and timeframe for submission and conduct of the study.

2. The competent authority of the Member State shall provide the marketing authorisation holder with an opportunity to present written observations in response to the imposition of the obligation within a time limit which it shall specify, if the marketing authorisation holder so requests within 30 days of receipt of the written notification of the obligation.

3. On the basis of the written observations submitted by the marketing authorisation holder, the competent authority of the Member State shall withdraw or confirm the obligation. Where the competent authority of the Member State confirms the obligation, the marketing authorisation shall be varied to include the obligation as a condition of the marketing authorisation and, where appropriate, the risk management system shall be updated accordingly.

Article 88

Delegated acts on post-authorisation efficacy studies

1. In order to determine the situations in which post-authorisation efficacy studies may be required under Articles 44 and 87, the Commission may adopt, by means of delegated acts in accordance with Article 215, measures supplementing the provisions in Articles 44 and 87.

2. When adopting such delegated acts, the Commission shall act in accordance with the provisions of this Directive.

Article 89

Recording of conditions related to marketing authorisations

1. The marketing authorisation holder shall incorporate any safety or efficacy conditions referred to in Articles 44, 45 and 87 in the risk management system.

2. The Member States shall inform the Agency of the marketing authorisations that they have granted subject to conditions pursuant to Articles 44, 45 and of any obligations imposed in accordance with Article 87.

Article 90

Update of marketing authorisation related to scientific and technological progress

1. After a marketing authorisation has been granted in accordance with Chapter III, the marketing authorisation holder shall, in respect of the methods of manufacture and control stated in the application for that marketing authorisation, take account of scientific and technical progress and introduce any changes that may be required to enable the medicinal product to be manufactured and controlled by means of generally accepted scientific methods.

   Those changes shall be subject to the approval of the competent authority of the Member State concerned.

2. The marketing authorisation holder shall without undue delay provide the competent authority of the Member State with any new information that might entail the amendment of the particulars or documentations referred to in Articles 6, 9 to 13, 62, 41(5), Annex I or Annex II.

   In particular, the marketing authorisation holder shall without undue delay inform the competent authority of the Member State of any prohibition or restriction imposed on the marketing authorisation holder or any entity in contractual relationship with the marketing authorisation holder by the competent authorities of any country in which the medicinal product is marketed and of any other new information that might influence the evaluation of the benefits and risks of the medicinal product concerned. The information shall include both positive and negative results of clinical trials or other studies in all therapeutic indications and populations, whether or not included in the marketing authorisation, as well as data on the use of the medicinal product where such use is outside the terms of the marketing authorisation.

3. The marketing authorisation holder shall ensure that the terms of the marketing authorisation including the summary of product characteristics, the labelling and package leaflet are kept up to date with current scientific knowledge, including the conclusions of the assessment and recommendations made publicly available by means of the European medicines web-portal set up in accordance with Article 104 of [revised Regulation (EC) No 726/2004].

4. The competent authority of the Member State may at any time request the marketing authorisation holder to submit data demonstrating that the benefit-risk balance remains favourable. The marketing authorisation holder shall answer fully and within the time limit set, any such request. The marketing authorisation holder shall also respond fully and within the time limit set to any request of a competent authority regarding the implementation of any measures previously imposed, including risk minimisation measures.

5. The competent authority of the Member State may at any time ask the marketing authorisation holder to submit a copy of the pharmacovigilance system master file. The marketing authorisation holder shall submit that copy at the latest seven days after receipt of the request.

6. The marketing authorisation holder shall also respond fully and within the time limit set to any request of a competent authority regarding the implementation of any measures previously imposed with regard to risks to the environment or public health, including antimicrobial resistance.

Article 91

Update of risk management plans

1. The marketing authorisation holder of a medicinal product referred to in Articles 9 and 11 shall submit to the competent authorities of the Member States concerned a risk management plan and a summary thereof, where the marketing authorisation for the reference medicinal product is withdrawn but the marketing authorisation for the medicinal product referred to in Articles 9 and 11 is maintained.

   The risk management plan and the summary thereof shall be submitted to the competent authorities of the Member States concerned within 60 days of the withdrawal of the marketing authorisation for the reference medicinal product by means of a variation.

2. The competent authority of the Member State may impose an obligation on a marketing authorisation holder for a medicinal product referred to Articles 9 and 11 to submit a risk management plan and summary thereof where:

   (a) additional risk minimisation measures have been imposed concerning the reference medicinal product; or

   (b) it is justified on pharmacovigilance grounds.

3. In the case referred to in paragraph 2, point (a), the risk management plan shall be aligned with the risk management plan for the reference medicinal product.

4. The imposition of the obligation referred to in paragraph 3 shall be duly justified in writing, notified to the marketing authorisation holder and shall include the deadline for submission of the risk management plan and the summary by means of a variation.

Article 92

Variation of marketing authorisation

1. An application for variation of a marketing authorisation by the marketing authorisation holder shall be made electronically in the formats made available by

the Agency, unless the variation is an update by the marketing authorisation holder of their information held in a database.

2. Variations shall be classified in different categories depending on the level of risk to public health and the potential impact on the quality, safety and efficacy of the medicinal product concerned. Those categories shall range from changes to terms of the marketing authorisation that have the highest potential impact on the quality, safety or efficacy of the medicinal product, to changes that have no or minimal impact thereon and to administrative changes.

3. The procedures for examination of applications for variations shall be proportionate to the risk and impact involved. Those procedures shall range from procedures that allow implementation only after approval based on a complete scientific assessment to procedures that allow immediate implementation and subsequent notification by the marketing authorisation holder to the competent authority. Such procedures may also include updates by the marketing authorisation holder of their information held in a database.

4. The Commission is empowered to adopt delegated acts in accordance with Article 215 to supplement this Directive by establishing the following:

   (a) the categories referred to in paragraph 2 in which variations shall be classified;

   (b) rules for the examination of applications for variations to the terms of marketing authorisations, including procedures for updates through a database;

   (c) the conditions for submission of a single application for more than one change to the terms of the same marketing authorisation and for the same change to the terms of several marketing authorisations;

   (d) specifying exemptions to the variation procedures where the update of information in the marketing authorisation referred to in Annex I may be directly implemented;

   (e) the conditions and procedures for cooperation with competent authorities of third countries or international organisations on examination of applications for variations to the terms of marketing authorisation.

Article 93

Variation of marketing authorisation under the decentralised or mutual recognition procedure

1. Any application by the marketing authorisation holder to vary a marketing authorisation that has been granted in accordance with the provisions of Chapter III, Sections 3 and 4, shall be submitted to all the Member States that have previously authorised the medicinal product concerned. The same shall apply where the initial marketing authorisations were granted through separate procedures.

2. In case of arbitration submitted to the Commission, the procedure laid down in Articles 41 and 42 shall apply by analogy to variations made to marketing authorisations.

Article 94

Variation of marketing authorisations on the basis of paediatric studies

1. On the basis of relevant paediatric clinical studies received in accordance with Article 45(1) of Regulation (EC) No 1901/2006 of the European Parliament and of the Council[39], the competent authorities of the Member States may vary the marketing authorisation of the medicinal product concerned accordingly and update the summary of product characteristics and package leaflet of the medicinal product concerned. The competent authorities shall exchange information regarding the studies submitted and, as appropriate, their implications for any marketing authorisations concerned.

2. The activities pursuant to paragraph 1 shall be concluded within five years from [OP please insert the date = 18 months after the date of entering into force of this Directive].

3. When a medicinal product has been authorised under the provisions of Chapter III, on the basis of the information received in accordance with Article 91 of [revised Regulation (EC) No 726/2004], the competent authorities of the Member States may vary the marketing authorisation of the medicinal product concerned accordingly and update the summary of product characteristics and package leaflet.

4. The Member States shall exchange information regarding the studies submitted and, as appropriate, their implications for any marketing authorisations concerned.

5. The Agency shall coordinate the exchange of information.

Article 95

Union interest referral procedure

1. The Member States or the Commission shall, in specific cases where the interests of the Union are involved, refer the matter to the Committee for Medicinal Products for Human Use for the application of the procedure laid down in Articles 41 and 42 before any decision is reached on an application for a marketing authorisation or on the suspension or revocation of a marketing authorisation, or on any other variation of the marketing authorisation that appears necessary. The Member States and the Commission shall take due account of any requests by the applicant or the marketing authorisation holder.

   Where the referral results from the evaluation of data relating to pharmacovigilance of an authorised medicinal product, the matter shall be referred to the Pharmacovigilance Risk Assessment Committee and Article 115(2) may be applied. The Pharmacovigilance Risk Assessment Committee shall issue a recommendation according to the procedure laid down in Article 41. The final recommendation shall be forwarded to the Committee for Medicinal Products for Human Use or to the coordination group, as appropriate, and the procedure laid down in Article 115 shall apply.

   However, where one of the criteria listed in Article 114(1) is met, the procedure laid down in Articles 114, 115 and 116 shall apply.

[39] Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 (OJ L 378, 27.12.2006, p. 1).

The Member State concerned or the Commission shall clearly identify the question that is referred to the Committee for consideration and shall inform the applicant or the marketing authorisation holder.

The Member States and the applicant or the marketing authorisation holder shall supply the Committee with all available information relating to the matter in question.

2. Where the referral to the Committee concerns a range of medicinal products or a therapeutic class, the Agency may limit the procedure to certain specific parts of the authorisation.

In that event, Article 93 shall apply to those medicinal products only if they were covered by the authorisation procedures referred to in Chapter III, Sections 3 and 4.

Where the scope of the procedure initiated under this Article concerns a range of medicinal products or a therapeutic class, medicinal products covered by a centralised marketing authorisation that belong to that range or class shall also be included in the procedure.

3. Without prejudice to paragraph 1, a Member State may, where urgent action is necessary to protect public health at any stage of the procedure, suspend the marketing authorisation and prohibit the use of the medicinal product concerned on its territory until a definitive decision is adopted. It shall inform the Commission, the Agency and the other Member States, no later than the following working day, of the reasons for its action.

4. Where the scope of the procedure initiated under this Article, as determined in accordance with paragraph 2, includes medicinal products covered by a centralised marketing authorisation, the Commission may, where urgent action is necessary to protect public health, at any stage of the procedure suspend the marketing authorisations and prohibit the use of the medicinal products concerned until a definitive decision is adopted. The Commission shall inform the Agency and the Member States no later than the following working day of the reasons for its action.

Chapter IX
Pharmacovigilance

SECTION 1

GENERAL PROVISIONS

Article 96

Member State pharmacovigilance system

1. Member States shall operate a pharmacovigilance system for the fulfilment of their pharmacovigilance tasks and their participation in the Union pharmacovigilance activities.

The pharmacovigilance system shall be used to collect information on the risks of medicinal products as regards health of the patients or the public. That information shall in particular refer to adverse reactions in human beings, arising from use of the medicinal product within the terms of the marketing authorisation as well as from use

outside the terms of the marketing authorisation, and to adverse reactions associated with occupational exposure.

2. Member States shall, by means of the pharmacovigilance system referred to in paragraph 1, evaluate all information scientifically, consider options for risk minimisation and prevention and take regulatory action concerning the marketing authorisation as necessary. They shall perform a regular audit of their pharmacovigilance system and take corrective actions if necessary.

3. Each Member State shall designate a competent authority for the performance of pharmacovigilance tasks.

4. The Commission may request the Member States to participate, under the coordination of the Agency, in international harmonisation and standardisation of technical measures in relation to pharmacovigilance.

Article 97

Member State responsibilities for pharmacovigilance activities

1. The Member States shall:

   (a) take all appropriate measures to encourage patients, doctors, pharmacists and other healthcare professionals to report suspected adverse reactions to the competent authority of the Member State and may involve organisations representing consumers, patients and healthcare professionals for those tasks where appropriate;

   (b) facilitate patient reporting through the provision of alternative reporting formats in addition to web-based formats;

   (c) take all appropriate measures to obtain accurate and verifiable data for the scientific evaluation of suspected adverse reaction reports;

   (d) ensure that the public is given important information on pharmacovigilance concerns relating to the use of a medicinal product in a timely manner through publication on the web-portal and through other means of publicly available information as necessary;

   (e) ensure, through the methods for collecting information and where necessary through the follow-up of suspected adverse reaction reports, that all appropriate measures are taken to identify clearly any biological medicinal product prescribed, dispensed, or sold in their territory that is the subject of a suspected adverse reaction report, with due regard to the name of the medicinal product, and the batch number.

2. For the purposes of paragraph 1, points (a) and (e), the Member States may impose specific obligations on doctors, pharmacists and other healthcare professionals.

Article 98

Member State delegation of pharmacovigilance tasks

1. A Member State may delegate any of the tasks entrusted to it under this Chapter to another Member State subject to a written agreement of the latter. Each Member State may represent no more than one other Member State.

2. The delegating Member State shall inform the Commission, the Agency and all other Member States of the delegation in writing. The delegating Member State and the Agency shall make that information publicly available.

Article 99

Marketing authorisation holder pharmacovigilance system

1. Marketing authorisation holders shall operate a pharmacovigilance system for the fulfilment of their pharmacovigilance tasks equivalent to the relevant Member State's pharmacovigilance system referred to in Article 96(1).

2. Marketing authorisation holders shall by means of the pharmacovigilance system referred to in Article 96(1) evaluate all information scientifically, consider options for risk minimisation and prevention and take appropriate measures as necessary.

3. Marketing authorisation holders shall perform a regular audit of their pharmacovigilance system. They shall place a note concerning the main findings of the audit on the pharmacovigilance system master file and, based on the audit findings, ensure that an appropriate corrective action plan is prepared and implemented. Once the corrective actions have been fully implemented, the note may be removed.

4. As part of the pharmacovigilance system, marketing authorisation holders shall:

   (a) have permanently and continuously at their disposal an appropriately qualified person responsible for pharmacovigilance;

   (b) maintain and make available on request by a competent authority a pharmacovigilance system master file;

   (c) operate a risk management system for each medicinal product;

   (d) monitor the outcome of risk minimisation measures that are contained in the risk management plan pursuant to Article 21 or that are laid down as conditions of the marketing authorisation pursuant to Articles 44, 45 and any obligations imposed in accordance with Article 87;

   (e) update the risk management system and monitor pharmacovigilance data to determine whether there are new risks or whether risks have changed or whether there are changes to the benefit-risk balance of medicinal products.

5. The qualified person referred to in paragraph 4, point (a), shall reside and operate in the Union and shall be responsible for the establishment and maintenance of the pharmacovigilance system. The marketing authorisation holder shall submit the name and contact details of the qualified person to the competent authority of the Member State and the Agency.

6. The marketing authorisation holder shall, on request from the competent authority of a Member State, nominate a contact person for pharmacovigilance issues in that Member State who shall report to the qualified person referred to in paragraph 4, point (a).

Article 100

Risk management system

1. Holders of marketing authorisations granted before 21 July 2012 shall, by way of derogation from Article 99(4), point (c), not be required to operate a risk management system for each medicinal product.

2. The competent authority of a Member State may impose an obligation on a marketing authorisation holder of a national marketing authorisation to operate a risk management system, as referred to in Article 99(4), point (c), if there are concerns about the risks affecting the benefit-risk balance of an authorised medicinal product. In that context, the competent authority of a Member State shall also oblige the marketing authorisation holder to submit a risk management plan for the risk management system that they intend to introduce for the medicinal product concerned.

3. The obligation referred to in paragraph 2 shall be duly justified, notified in writing, and shall include the timeframe for submission of the risk management plan.

4. The competent authority of a Member State shall provide the marketing authorisation holder with an opportunity to submit written observations in response to the imposition of the obligation within a time limit which it shall specify, if the marketing authorisation holder so requests within 30 days of receipt of the written notification of the obligation.

5. On the basis of the written observations submitted by the marketing authorisation holder, the competent authority of a Member State shall withdraw or confirm the obligation. Where the competent authority of a Member State confirms the obligation, the marketing authorisation shall be varied accordingly to include the measures to be taken as part of the risk management system as conditions of the marketing authorisation referred to in Article 44, point (a).

Article 101

Funds for pharmacovigilance activities

1. The management of funds intended for activities connected with pharmacovigilance, the operation of communication networks and market surveillance shall be under the permanent control of the competent authorities of the Member States in order to guarantee their independence in the performance of those pharmacovigilance activities.

2. Paragraph 1 shall not preclude the competent authorities of the Member States from charging fees to marketing authorisation holders for performing pharmacovigilance activities on the condition that the independence in the performance of those pharmacovigilance activities is strictly guaranteed.

SECTION 2

TRANSPARENCY AND COMMUNICATIONS

Article 102

National web-portal

1. Each Member State shall set up and maintain a national medicines web-portal which shall be linked to the European medicines web-portal established in accordance with Article 104 of [revised Regulation (EC) No 726/2004]. By means of the national

medicines web-portals, the Member States shall make publicly available at least the following:

(a) public assessment reports, together with a summary thereof;

(b) summaries of product characteristics and package leaflets;

(c) summaries of risk management plans for medicinal products covered by a national marketing authorisation in accordance with Chapter III;

(d) information on the different ways of reporting suspected adverse reactions to medicinal products to competent authorities of the Member States by healthcare professionals and patients, including the web-based structured forms referred to in Article 102 of [revised Regulation (EC) No 726/2004].

2. The summaries referred to in paragraph 2, point (c), shall include, where relevant, a description of additional risk minimisation measures.

Article 103

Publication of assessment

The Agency shall make publicly available the final assessment conclusions, recommendations, opinions and decisions referred to in Articles 107 to 116, by means of the European medicines web-portal.

Article 104

Public announcements

1. As soon as the marketing authorisation holder intends to make a public announcement relating to information on pharmacovigilance concerns in relation to the use of a medicinal product, and in any event at the same time or before the public announcement is made, they shall be required to inform the competent authorities of the Member States, the Agency and the Commission.

2. The marketing authorisation holder shall ensure that information to the public is presented objectively and is not misleading.

3. Unless urgent public announcements are required for the protection of public health, the Member States, the Agency and the Commission shall inform each other not less than 24 hours prior to a public announcement relating to information on pharmacovigilance concerns.

4. For active substances contained in medicinal products authorised in more than one Member State, the Agency shall be responsible for the coordination between competent authorities of the Member States of safety announcements and shall provide timetables for the information being made publicly available.

5. Under the coordination of the Agency, the Member States shall make all reasonable efforts to agree on a common message in relation to the safety of the medicinal product concerned and the timetables for their distribution. The Pharmacovigilance Risk Assessment Committee shall, at the request of the Agency, provide advice on those safety announcements.

6. When the Agency or competent authorities of the Member States make publicly available information referred to in paragraphs 2 and 3, any personal data or data of a

commercially confidential nature shall be deleted unless its public disclosure is necessary for the protection of public health.

SECTION 3

RECORDING AND REPORTING OF SUSPECTED ADVERSE REACTIONS

Article 105

Recording and reporting of suspected adverse reactions by the marketing authorisation holder

1. Marketing authorisation holders shall record all suspected adverse reactions in the Union or in third countries that are brought to their attention, whether reported spontaneously by patients or healthcare professionals, or occurring in the context of a post-authorisation study including data relating to off-label use of the product.

   Marketing authorisation holders shall ensure that those reports are accessible at a single point within the Union.

   By way of derogation from the first subparagraph, suspected adverse reactions occurring in the context of a clinical trial shall be recorded and reported in accordance with Regulation (EU) No 536/2014.

2. Marketing authorisation holders shall not refuse to consider reports of suspected adverse reactions received electronically or by any other appropriate means from patients or healthcare professionals.

3. Marketing authorisation holders shall submit electronically to the database and data-processing network referred to in Article 101 of [revised Regulation (EC) No 726/2004] ('Eudravigilance database') information on all serious suspected adverse reactions that occur in the Union and in third countries within 15 days following the day on which the marketing authorisation holder concerned gained knowledge of the event.

   Marketing authorisation holders shall submit electronically to the Eudravigilance database information on all non-serious suspected adverse reactions that occur in the Union, within 90 days following the day on which the marketing authorisation holder concerned gained knowledge of the event.

   For medicinal products containing active substances referred to in the list of publications monitored by the Agency pursuant to Article 105 of [revised Regulation (EC) No 726/2004], marketing authorisation holders shall not be required to report to the Eudravigilance database the suspected adverse reactions recorded in the listed publications, but they shall monitor all other medical literature and report any suspected adverse reactions recorded therein.

4. Marketing authorisation holders shall establish procedures in order to obtain accurate and verifiable data for the scientific evaluation of suspected adverse reaction reports. They shall also collect follow-up information on those reports and submit the updates to the Eudravigilance database.

5. Marketing authorisation holders shall collaborate with the Agency and the competent authorities of the Member States in the detection of duplicates of suspected adverse reaction reports.

6. This Article shall apply *mutatis mutandis* to undertakings supplying medicinal products used in accordance with Article 3, paragraphs 1 or 2.

Article 106

Recording and reporting of suspected adverse reactions by Member States

1. Each Member State shall record all suspected adverse reactions that occur in its territory and that are brought to its attention from healthcare professionals and patients. This shall include all authorised medicinal products and medicinal products used in accordance with Article 3, paragraphs 1 or 2. Member States shall involve patients and healthcare professionals, as appropriate, in the follow-up of any reports they receive in order to comply with Article 97(1), points (c) and (e).

   Member States shall ensure that reports of such reactions may be submitted by means of the national medicines web-portals or by other means.

2. For reports submitted by a marketing authorisation holder, Member States on whose territory the suspected adverse reaction occurred may involve the marketing authorisation holder in the follow-up of the reports.

3. Member States shall collaborate with the Agency and the marketing authorisation holders in the detection of duplicates of suspected adverse reaction reports.

4. Member States shall, within 15 days following the receipt of the reports of serious suspected adverse reactions referred to in paragraph 1, submit the reports electronically to the Eudravigilance database.

   Member States shall, within 90 days from the receipt of the reports referred to in paragraph 1, submit reports of non-serious suspected adverse reactions electronically to the Eudravigilance database.

   Marketing authorisation holders shall have access to the reports referred to in this paragraph through the Eudravigilance database.

5. Member States shall ensure that reports of suspected adverse reactions arising from an error associated with the use of a medicinal product that are brought to their attention are made available to the Eudravigilance database and to any authorities, bodies, organisations or institutions, responsible for patient safety within that Member State concerned. They shall also ensure that the authorities responsible for medicinal products within that Member State are informed of any suspected adverse reactions brought to the attention of any other authority within that Member State. These reports shall be appropriately identified in the forms referred to in Article 102 of [revised Regulation (EC) No 726/2004].

6. Unless there are justifiable grounds resulting from pharmacovigilance activities, Member States shall not impose any additional obligations on marketing authorisation holders for the reporting of suspected adverse reactions.

SECTION 4

PERIODIC SAFETY UPDATE REPORTS

Article 107

Periodic safety update reports

1. Marketing authorisation holders shall submit to the Agency periodic safety update reports containing:

(a) summaries of data relevant to the benefit-risk balance of the medicinal product, including results of all studies with a consideration of their potential impact on the marketing authorisation;

(b) a scientific evaluation of the benefit-risk balance of the medicinal product;

(c) all data relating to the volume of sales of the medicinal product and any data in possession of the marketing authorisation holder relating to the volume of prescriptions, including an estimate of the population exposed to the medicinal product.

The data provided in accordance with the first subparagraph, point (c), shall differentiate between sales and volumes generated within the Union and those generated outside the Union.

2. The evaluation referred to in paragraph 1, first subparagraph, point (b), shall be based on all available data, including data from clinical trials in unauthorised therapeutic indications and populations.

The periodic safety update reports shall be submitted electronically.

3. The Agency shall make available the reports referred to in paragraph 1 to the competent authorities of the Member States, the members of the Pharmacovigilance Risk Assessment Committee, the Committee for Medicinal Products for Human Use and the coordination group by means of the repository referred to in Article 103 of [revised Regulation (EC) No 726/2004].

4. By way of derogation from paragraph 1, the marketing authorisation holders for medicinal products referred to in Articles 9, or 13, and the registration holders for medicinal products referred to in Articles 126 or 134(1), shall only be required to submit periodic safety update reports for such medicinal products to the competent authority in the following cases:

(a) where such obligation has been laid down as a condition in the marketing authorisation in accordance with Articles 44 or 45; or

(b) when requested by a competent authority on the basis of concerns relating to pharmacovigilance data or due to the lack of periodic safety update reports relating to an active substance after the marketing authorisation has been granted.

The assessment reports of the periodic safety update reports referred to in the first subparagraph shall be communicated by the competent authority to the Pharmacovigilance Risk Assessment Committee, which shall consider whether there is a need for a single assessment report for all marketing authorisations for medicinal products containing the same active substance and which shall inform the coordination group or the Committee for Medicinal Products for Human Use accordingly, in order to apply the procedures laid down in Articles 108(4) and 110.

Article 108

Frequency of periodic safety update reports

1. The frequency with which the periodic safety update reports are to be submitted shall be specified in the marketing authorisation.

The dates of submission according to the specified frequency shall be calculated from the date when then marketing authorisation was granted.

2. Holders of marketing authorisations which have been granted before 21 July 2012, and for which the frequency and dates of submission of the periodic safety update reports are not laid down as a condition to the marketing authorisation, shall submit the periodic safety update reports in accordance with the second subparagraph until another frequency or other dates of submission of the reports are laid down in the marketing authorisation or determined in accordance with the paragraphs 4, 5 and 6.

Periodic safety update reports shall be submitted to the competent authorities immediately upon request:

(a) where a medicinal product has not yet been placed on the market, at least every six months following the marketing authorisation and until the placing on the market;

(b) where a medicinal product has been placed on the market, at least every six months during the first two years following the initial placing on the market, once a year for the following two years and at three-yearly intervals thereafter.

3. Paragraph 2 shall also apply to medicinal products that are authorised only in one Member State and for which paragraph 4 does not apply.

4. Where medicinal products that are subject to different marketing authorisations contain the same active substance or the same combination of active substances, the frequency and dates of submission of the periodic safety update reports resulting from the application of the paragraphs 1 and 2 may be amended and harmonised to enable a single assessment to be made in the context of a periodic safety update report work-sharing procedure and to set a Union reference date from which the submission dates to be calculated.

The harmonised frequency for the submission of the reports and the Union reference date may be determined, after consultation of the Pharmacovigilance Risk Assessment Committee, by one of the following:

(a) the Committee for Medicinal Products for Human Use, where at least one of the marketing authorisations for the medicinal products containing the active substance concerned has been granted in accordance with the centralised procedure provided for in Article 3 of [revised Regulation (EC) No 726/2004];

(b) the coordination group, in other cases than those referred to in point (a).

The harmonised frequency for the submission of the reports determined pursuant to the first and second subparagraphs shall be made publicly available by the Agency. Marketing authorisation holders shall submit an application for a variation of the marketing authorisation accordingly.

5. For the purposes of paragraph 4, the Union reference date for medicinal products containing the same active substance or the same combination of active substances shall be one of the following:

(a) the date when the first marketing authorisation was granted in the Union for a medicinal product containing that active substance or that combination of active substances;

(b) if the date referred to in point (a) cannot be ascertained, the earliest of the known dates of the marketing authorisations for a medicinal product containing that active substance or that combination of active substances.

6. Marketing authorisation holders shall be allowed to submit requests to the Committee for Medicinal Products for Human Use or the coordination group, as appropriate, to determine Union reference dates or to change the frequency of submission of periodic safety update reports on one of the following grounds:

(a) for reasons relating to public health;

(b) in order to avoid a duplication of the assessment;

(c) in order to achieve international harmonisation.

Such requests shall be submitted in writing and shall be duly justified. The Committee for Medicinal Products for Human Use or the coordination group shall, following the consultation with the Pharmacovigilance Risk Assessment Committee, either approve or deny such requests. Any change in the dates or the frequency of submission of periodic safety update reports shall be made publicly available by the Agency. The marketing authorisation holders shall submit an application for a variation of the marketing authorisation accordingly.

7. The Agency shall make public a list of Union reference dates and frequency of submission of periodic safety update reports by means of the European medicines web-portal.

Any change to the dates of submission and frequency of periodic safety update reports specified in the marketing authorisation as a result of the application of the paragraphs 4, 5 and 6 shall take effect four months after the date of the publication referred to in the first subparagraph.

Article 109

Assessment of periodic safety update reports

The competent authorities of the Member State shall assess periodic safety update reports to determine whether there are new risks or whether risks have changed or whether there are changes to the benefit-risk balance of medicinal products.

Article 110

Single assessment of periodic safety update reports

1. A single assessment of periodic safety update reports shall be performed for medicinal products authorised in more than one Member State and, in the cases referred to in Article 108, paragraphs 4, 5 and 6, for all medicinal products containing the same active substance or the same combination of active substances and for which a Union reference date and a frequency of periodic safety update reports has been established.

The single assessment shall be conducted by either of the following:

(a) a Member State appointed by the coordination group where none of the marketing authorisations concerned has been granted in accordance with the centralised procedure provided for in Article 3 of [revised Regulation (EC) No 726/2004];

(b) a rapporteur appointed by the Pharmacovigilance Risk Assessment Committee, where at least one of the marketing authorisations concerned has been granted in accordance with the centralised procedure provided for in Article 3 of [revised Regulation (EC) No 726/2004].

When selecting the Member State in accordance with the second subparagraph, point (a), the coordination group shall take into account whether any Member State is acting as a reference Member State, in accordance with Chapter III, Sections 3 and 4.

2. The Member State or rapporteur, as appropriate, shall prepare an assessment report within 60 days of receipt of the periodic safety update report and send it to the Agency and to the Member States concerned. The Agency shall send the report to the marketing authorisation holder.

Within 30 days of receipt of the assessment report, the Member States and the marketing authorisation holder may submit comments to the Agency and to the rapporteur or Member State.

3. Following the receipt of the comments referred to in paragraph 2, the rapporteur or Member State shall within 15 days update the assessment report taking into account any comments submitted, and forward it to the Pharmacovigilance Risk Assessment Committee. The Pharmacovigilance Risk Assessment Committee shall adopt the assessment report with or without further changes at its next meeting and issue a recommendation. The recommendation shall mention any divergent positions with the grounds on which they are based. The Agency shall include the adopted assessment report and the recommendation in the repository set up under Article 103 of [revised Regulation (EC) No 726/2004] and forward them to the marketing authorisation holder.

Article 111

Regulatory action on periodic safety update reports

Following the assessment of periodic safety update reports referred to in Article 107, the competent authorities of the Member States shall consider whether any action concerning the marketing authorisation for the medicinal product concerned is necessary and shall maintain, vary, suspend or revoke the marketing authorisation as appropriate.

Article 112

Procedure for regulatory action on periodic safety update reports

1. In the case of a single assessment of periodic safety update reports in accordance with Article 110(1) which recommends action concerning more than one marketing authorisation that does not include any centralised marketing authorisation, the coordination group shall, within 30 days of receipt of the assessment report of the Pharmacovigilance Risk Assessment Committee, consider the assessment report and reach a position on the maintenance, variation, suspension or revocation of the marketing authorisations concerned, including a timetable for the implementation of the agreed position.

2. If, within the coordination group, the Member States represented reach an agreement on the action to be taken by consensus, the chairperson shall record the agreement and send it to the marketing authorisation holder and the Member States. The Member States shall adopt necessary measures to maintain, vary, suspend or revoke

the marketing authorisations concerned in accordance with the timetable for implementation determined in the agreement.

In the event of a variation, the marketing authorisation holder shall submit to the competent authorities of the Member States an appropriate application for a modification, including an updated summary of product characteristics and an updated package leaflet within the determined timetable for implementation.

If an agreement by consensus cannot be reached, the position of the majority of the Member States represented within the coordination group shall be forwarded to the Commission which shall apply the procedure laid down in Article 42.

Where the agreement reached by the Member States represented within the coordination group or the position of the majority of Member States differs from the recommendation of the Pharmacovigilance Risk Assessment Committee, the coordination group shall attach to the agreement or the majority position a detailed explanation of the scientific grounds for the differences together with the recommendation.

3. In the case of a single assessment of periodic safety update reports in accordance with Article 110(1) that recommends action concerning more than one marketing authorisation that includes at least one centralised marketing authorisation, the Committee for Medicinal Products for Human Use shall, within 30 days of receipt of the report of the Pharmacovigilance Risk Assessment Committee, consider the report and adopt an opinion on the maintenance, variation, suspension or revocation of the marketing authorisations concerned, including a timetable for the implementation of the opinion.

4. Where the opinion of the Committee for Medicinal Products for Human Use referred to in paragraph 3 differs from the recommendation of the Pharmacovigilance Risk Assessment Committee, the Committee for Medicinal Products for Human Use shall attach to its opinion a detailed explanation of the scientific grounds for the differences together with the recommendation.

5. On the basis of the opinion of the Committee for Medicinal Products for Human Use referred to in paragraph 3, the Commission shall, by means of implementing acts:

   (a) adopt a decision addressed to the Member States concerning the measures to be taken in respect of marketing authorisations granted by the Member States and concerned by the procedure provided for in this section; and

   (b) where the opinion states that regulatory action concerning the marketing authorisation is necessary, adopt a decision to vary, suspend or revoke the centralised marketing authorisations and concerned by the procedure provided for in this section.

6. Article 42 shall apply to the adoption of the decision referred to in paragraph 5, point (a), and to its implementation by the Member States.

7. Article 13 of [revised Regulation (EC) No 726/2004] shall apply to the decision referred to in paragraph 5, point (b). Where the Commission adopts such decision, it may also adopt a decision addressed to the Member States pursuant to Article 55 of [revised Regulation (EC) No 726/2004].

SECTION 5

SIGNAL DETECTION

Article 113

Signal monitoring and detection

1. Regarding medicinal products authorised in accordance with Chapter III, competent authorities of the Member States shall in collaboration with the Agency, take the following measures:

   (a) monitor the outcome of risk minimisation measures contained in risk management plans and of the conditions referred to in Articles 44, 45 and any obligations imposed in accordance with Article 87;

   (b) assess updates to the risk management system;

   (c) monitor the data in the Eudravigilance database to determine whether there are new risks or whether risks have changed and whether those risks impact on the benefit-risk balance.

2. The Pharmacovigilance Risk Assessment Committee shall perform the initial analysis and prioritisation of signals of new risks or risks that have changed or changes to the benefit-risk balance. Where it considers that follow-up action may be necessary, the assessment of those signals and agreement on any subsequent action concerning the marketing authorisation shall be conducted in a timescale commensurate with the extent and seriousness of the issue.

3. The Agency and competent authorities of the Member States and the marketing authorisation holder shall inform each other in the event of new risks or risks that have changed or changes to the benefit-risk balance being detected.

4. Member States shall ensure that marketing authorisation holders inform the Agency and competent authorities of the Member State in the event of new risks or risks that have changed or when changes to the benefit-risk balance have been detected.

SECTION 6

URGENT UNION PROCEDURE

Article 114

Initiation of an urgent Union procedure

1. A Member State or the Commission, as appropriate, shall, on the basis of concerns resulting from the evaluation of data from pharmacovigilance activities, initiate the procedure provided for in this Section (the ‘urgent Union procedure’) by informing the other Member States, the Agency and the Commission where:

   (a) it considers suspending or revoking a marketing authorisation;

   (b) it considers prohibiting the supply of a medicinal product;

   (c) it considers refusing the renewal of a marketing authorisation; or

(d) it is informed by the marketing authorisation holder that, on the basis of safety concerns, the marketing authorisation holder has interrupted the placing on the market of a medicinal product or has taken action to have a marketing authorisation withdrawn, or intends to take such action or has not applied for the renewal of a marketing authorisation.

2. A Member State or the Commission, as appropriate, shall, on the basis of concerns resulting from the evaluation of data from pharmacovigilance activities, inform the other Member States, the Agency and the Commission where it considers that a new contraindication, a reduction in the recommended dose or a restriction to the therapeutic indications of a medicinal product is necessary. The information shall outline the action considered and the reasons therefore.

Any Member State or the Commission, as appropriate, shall, when urgent action is considered necessary in any of the cases referred to in the first subparagraph, initiate the urgent Union procedure.

Where the urgent Union procedure is not initiated, for medicinal products authorised in accordance with Chapter III, Sections 3 and 4, the case shall be brought to the attention of the coordination group.

Article 95 shall apply where the interests of the Union are involved.

3. Where the urgent Union procedure is initiated, the Agency shall verify whether the safety concern relates to medicinal products other than the one covered by the information, or whether the safety concern is common to all medicinal products belonging to the same range or therapeutic class.

Where the medicinal product involved is authorised in more than one Member State, the Agency shall without undue delay inform the initiator of the urgent Union procedure of the outcome of the verification, and the procedures laid down in Articles 115 and 116 shall apply. Otherwise, the safety concern shall be addressed by the Member State concerned. The Agency or the Member State, as applicable, shall make the information that the urgent Union procedure has been initiated available to marketing authorisation holders.

4. Without prejudice to paragraphs 1 and 2, and Articles 115 and 116, a Member State may, where urgent action is necessary to protect public health, suspend the marketing authorisation and prohibit the use of the medicinal product concerned on its territory until a definitive decision is adopted in the urgent Union procedure. It shall inform the Commission, the Agency and the other Member States no later than the following working day of the reasons for its action.

5. At any stage of the procedure laid down in Articles 115 and 116, the Commission may request a Member State in which the medicinal product is authorised to take temporary measures immediately.

Where the scope of the procedure, as determined in accordance with paragraphs 1 and 2, includes medicinal products covered by centralised marketing authorisations, the Commission may, at any stage of the urgent Union procedure, take temporary measures immediately in relation to those marketing authorisations.

6. The information referred to in this Article may relate to individual medicinal products or to a range of medicinal products or a therapeutic class.

If the Agency identifies that the safety concern relates to more medicinal products than those that are covered by the information or that the safety concern is common

to all medicinal products belonging to the same range or therapeutic class, it shall extend the scope of the procedure accordingly.

Where the scope of the urgent Union procedure concerns a range of medicinal products or therapeutic class, medicinal products covered by the centralised marketing authorisation, that belong to that range or class shall also be included in the procedure.

7. At the time the information referred to in paragraphs 1 and 2 is provided, the Member State shall make available to the Agency all relevant scientific information that it has at its disposal and any assessment by the Member State.

Article 115

Urgent Union procedure scientific assessment

1. Following receipt of the information referred to in Article 114, paragraphs 1 and 2, the Agency shall publicly announce the initiation of the urgent Union procedure by means of the European medicines web-portal. In parallel, Member States may publicly announce the initiation of the procedure on their national medicines web-portals.

   The announcement shall specify the matter submitted to the Agency in accordance with Article 114, and the medicinal products and, where applicable, the active substances concerned. It shall contain information on the right of the marketing authorisation holders, healthcare professionals and the public to submit to the Agency information relevant to the procedure and it shall state how such information may be submitted.

2. The Pharmacovigilance Risk Assessment Committee shall assess the matter that has been submitted to the Agency in accordance with Article 114. The rapporteur, as referred to in Article 152 of [revised Regulation (EC) No 726/2004], shall closely collaborate with the rapporteur appointed by the Committee for Medicinal Products for Human Use and with the reference Member State for the medicinal products concerned.

   For the purposes of the assessment referred to in the first subparagraph, the marketing authorisation holder may submit comments in writing.

   Where the urgency of the matter permits, the Pharmacovigilance Risk Assessment Committee may hold public hearings, where it considers that this is appropriate on justified grounds particularly with regard to the extent and seriousness of the safety concern. The hearings shall be held in accordance with the modalities specified by the Agency and shall be announced by means of the European medicines web-portal. The announcement shall specify the modalities of participation.

   The Agency shall, in consultation with the parties concerned, draw up Rules of Procedure on the organisation and conduct of public hearings, in accordance with Article 163 of [revised Regulation (EC) No 726/2004].

   Where a marketing authorisation holder or another person intending to submit information, has confidential data relevant to the subject matter of the procedure, they may request permission to present that data to the Pharmacovigilance Risk Assessment Committee in a non-public hearing.

3. Within 60 days of the submission of the information, the Pharmacovigilance Risk Assessment Committee shall make a recommendation, stating the reasons on which it is based, having due regard to the therapeutic effect of the medicinal product. The recommendation shall mention any divergent positions and the grounds on which they are based. In the case of urgency, and on the basis of a proposal by its chairperson, the Pharmacovigilance Risk Assessment Committee may agree to a shorter deadline. The recommendation shall include any or a combination of the following conclusions:

   (a) no further evaluation or action is required at Union level;

   (b) the marketing authorisation holder should conduct further evaluation of data and carry out a follow-up of the results of that evaluation;

   (c) the marketing authorisation holder should sponsor a post-authorisation safety study and carry out a follow up evaluation of the results of that study;

   (d) the Member States or marketing authorisation holder should implement risk minimisation measures;

   (e) the marketing authorisation should be suspended, revoked or not renewed;

   (f) the marketing authorisation should be varied.

4. For the purposes of paragraph 3, point (d), the recommendation shall specify the risk minimisation measures recommended and any conditions or restrictions to which the marketing authorisation should be made subject, including the timeline for implementation.

5. For the purposes of paragraph 3, point (f), where it is recommended to change or add information in the summary of product characteristics or the labelling or package leaflet, the recommendation shall suggest the wording of such changed or added information and shall indicate where in the summary of product characteristics, the labelling or package leaflet such wording should be placed.

Article 116

Follow-up of recommendation made in the framework of the urgent Union procedure

1. Where the scope of the urgent Union procedure, as determined in accordance with Article 114(6), does not include any centralised marketing authorisation, the coordination group shall, within 30 days of receipt of the recommendation of the Pharmacovigilance Risk Assessment Committee, consider the recommendation and reach a position on the maintenance, variation, suspension, revocation or refusal of the renewal of the marketing authorisation concerned, including a timetable for the implementation of the agreed position. Where an urgent adoption of the position is necessary, the coordination group may, on the basis of a proposal by its chairperson, agree to a shorter deadline.

2. If, within the coordination group, the Member States represented reach an agreement on the action to be taken by consensus, the chairperson shall record the agreement and send it to the marketing authorisation holder and the Member States. The Member States shall adopt necessary measures to maintain, vary, suspend, revoke or refuse renewal of the marketing authorisation concerned in accordance with the implementation timetable determined in the agreement.

In the event that a variation is agreed upon, the marketing authorisation holder shall submit to the competent authorities of the Member States an appropriate application for a variation, including an updated summary of product characteristics and an updated package leaflet within the determined timetable for implementation.

If an agreement by consensus cannot be reached, the position of the majority of the Member States represented within the coordination group shall be forwarded to the Commission which shall apply the procedure laid down in Article 42.

Where the agreement reached by the Member States represented within the coordination group or the position of the majority of the Member States represented within the coordination group differs from the recommendation of the Pharmacovigilance Risk Assessment Committee, the coordination group shall attach to the agreement or majority position a detailed explanation of the scientific grounds for the differences together with the recommendation.

3. Where the scope of the procedure, as determined in accordance with Article 114(6), includes at least one centralised marketing authorisation, the Committee for Medicinal Products for Human Use shall, within 30 days of receipt of the recommendation of the Pharmacovigilance Risk Assessment Committee, consider the recommendation and adopt an opinion on the maintenance, variation, suspension, revocation or refusal of the renewal of the marketing authorisations concerned. Where an urgent adoption of the opinion is necessary, the Committee for Medicinal Products for Human Use may, on the basis of a proposal by its chairperson, agree to a shorter deadline.

   Where the opinion of the Committee for Medicinal Products for Human Use differs from the recommendation of the Pharmacovigilance Risk Assessment Committee, the Committee for Medicinal Products for Human Use shall attach to its opinion a detailed explanation of the scientific grounds for the differences together with the recommendation.

4. On the basis of the opinion of the Committee for Medicinal Products for Human Use referred to in paragraph 3, the Commission shall, by means of implementing acts:

   (a) adopt a decision addressed to the Member States concerning the measures to be taken in respect of marketing authorisations that are granted by the Member States and that are subject to the urgent Union procedure;

   (b) where the opinion states that regulatory action concerning the marketing authorisation is necessary, adopt a decision to vary, suspend, revoke or refuse the renewal of the centralised marketing authorisations and concerned by the procedure provided for in this section.

5. Article 42 shall apply to the adoption of the decision referred to in paragraph 4, point (a), and to its implementation by the Member States.

6. Article 13 of [revised Regulation (EC) No 726/2004] shall apply to the decision referred to in paragraph 4, point (b). Where the Commission adopts such decision, it may also adopt a decision addressed to the Member States pursuant to Article 55 of [revised Regulation (EC) No 726/2004].

SECTION 7

SUPERVISION OF POST-AUTHORISATION SAFETY STUDIES

Article 117

Non-interventional post-authorisation safety studies

1. This Section applies to non-interventional post-authorisation safety studies that are initiated, managed or financed by the marketing authorisation holder voluntarily or pursuant to obligations imposed in accordance with Articles 44 or 87, and that involve the collection of safety data from patients or healthcare professionals.

2. This Section is without prejudice to Member States and Union requirements for ensuring the well-being and rights of participants in non-interventional post-authorisation safety studies.

3. The studies shall not be performed where the act of conducting the study promotes the use of a medicinal product.

4. Payments to healthcare professionals for participating in non-interventional post-authorisation safety studies shall be restricted to the compensation for time and expenses incurred.

5. The competent authority of the Member State may require the marketing authorisation holder to submit the protocol and the progress reports to the competent authorities of the Member States in which the study is conducted.

6. The marketing authorisation holder shall send the final report of the study to the competent authorities of the Member States in which the study was conducted within 12 months of the end of data collection.

7. While a study is being conducted, the marketing authorisation holder shall monitor the data generated and consider its implications for the benefit-risk balance of the medicinal product concerned.

   Any new information that might influence the evaluation of the benefit-risk balance of the medicinal product shall be communicated to the competent authorities of the Member State in which the medicinal product has been authorised in accordance with Article 90.

   The obligation laid down in the second subparagraph is without prejudice to the information on the results of studies that the marketing authorisation holder shall make available by means of the periodic safety update reports as laid down in Article 107.

8. Articles 118 to 121 shall apply exclusively to studies referred to in paragraph 1 that are conducted pursuant to an obligation imposed in accordance with Articles 44 or 87.

Article 118

Agreement of a protocol for a non-interventional post-authorisation safety study

1. Before a study is conducted, the marketing authorisation holder shall submit a draft protocol to the Pharmacovigilance Risk Assessment Committee, except for studies to be conducted in only one Member State that requests the study in accordance with

Article 87. For such studies, the marketing authorisation holder shall submit a draft protocol to the competent authority of the Member State in which the study is conducted.

2. Within 60 days of the submission of the draft protocol referred to in paragraph 1 the competent authority of the Member State or the Pharmacovigilance Risk Assessment Committee, as appropriate, shall issue:

(a) a letter endorsing the draft protocol;

(b) a letter of objection, which shall set out in detail the grounds for the objection, where:

(i) it considers that the conduct of the study promotes the use of a medicinal product;

(ii) it considers that the design of the study does not fulfil the study objectives; or

(c) a letter notifying the marketing authorisation holder that the study is a clinical trial falling under the scope of Regulation (EU) No 536/2014.

3. The study may commence only when the written endorsement from the competent authority of the Member State or the Pharmacovigilance Risk Assessment Committee, as appropriate, has been issued.

Where a letter of endorsement of the draft protocol as referred to in paragraph 2, point (a), has been issued, the marketing authorisation holder shall forward the protocol to the competent authorities of the Member States in which the study is to be conducted and may thereafter commence the study according to the endorsed protocol.

Article 119

Update of a protocol for a non-interventional post-authorisation safety study

After a study has been commenced, any substantial amendments to the protocol shall be submitted, before their implementation, to the competent authority of the Member State or to the Pharmacovigilance Risk Assessment Committee, as appropriate. The competent authority of the Member State or the Pharmacovigilance Risk Assessment Committee, as appropriate, shall assess the amendments and inform the marketing authorisation holder of its endorsement or objection. Where applicable, the marketing authorisation holder shall inform the Member States in which the study is conducted.

Article 120

Final study report on a non-interventional post-authorisation safety study

1. Upon completion of the study, a final study report shall be submitted to the competent authority of the Member State or the Pharmacovigilance Risk Assessment Committee within 12 months of the end of data collection unless a written waiver has been granted by the competent authority of the Member State or the Pharmacovigilance Risk Assessment Committee, as appropriate.

2. The marketing authorisation holder shall evaluate whether the results of the study have an impact on the marketing authorisation and shall, if necessary, submit to the

competent authorities of the Member States an application to vary the marketing authorisation.

3. Together with the final study report, the marketing authorisation holder shall electronically submit an abstract of the study results to the competent authority of the Member State or the Pharmacovigilance Risk Assessment Committee.

Article 121

Recommendations following the submission of a final study report on non-interventional post-authorisation safety studies

1. Based on the results of the study and after consultation of the marketing authorisation holder, the Pharmacovigilance Risk Assessment Committee may make recommendations concerning the marketing authorisation, stating the reasons on which they are based. The recommendations shall mention any divergent positions and the grounds on which they are based.

2. When recommendations for the variation, suspension or revocation of a national marketing authorisation are made, the Member States represented within the coordination group shall agree on a position on the matter taking into account the recommendation referred to in paragraph 1 and shall include a timetable for the implementation of the agreed position.

   If, within the coordination group, the Member States represented reach an agreement on the action to be taken by consensus, the chairperson shall record the agreement and send it to the marketing authorisation holder and the Member States. The Member States shall adopt necessary measures to vary, suspend or revoke the marketing authorisation concerned in accordance with the implementation timetable determined in the agreement.

   In the event that a variation is agreed upon, the marketing authorisation holder shall submit to the competent authorities of the Member State an appropriate application for a variation, including an updated summary of product characteristics and an updated package leaflet within the determined timetable for implementation.

   The agreement shall be made publicly available on the European medicines web-portal established in accordance with Article 104 of [revised Regulation (EC) No 726/2004].

3. If an agreement by consensus cannot be reached, the position of the majority of the Member States represented within the coordination group shall be forwarded to the Commission, which shall apply the procedure laid down in Article 42.

4. Where the agreement reached by the Member States represented within the coordination group or the position of the majority of Member States differs from the recommendation of the Pharmacovigilance Risk Assessment Committee, the coordination group shall attach to the agreement or majority position a detailed explanation of the scientific grounds for the differences together with the recommendation.

SECTION 8

IMPLEMENTATION, GUIDANCE AND REPORTING

Article 122

Implementing measures related to pharmacovigilance activities

1. In order to harmonise the performance of the pharmacovigilance activities provided for in this Directive, the Commission shall adopt implementing measures in the following areas for which pharmacovigilance activities are provided for in Annex I, Articles 96, 99, 100, 105 to 107, 113, 118 and 120 by setting out:

   (a) the content and the rules on the maintenance of the pharmacovigilance system master file kept by the marketing authorisation holder;

   (b) minimum requirements for the quality system for the performance of pharmacovigilance activities by the competent authorities of the Member States and the marketing authorisation holder;

   (c) rules on the use of internationally agreed terminology, formats and standards for the performance of pharmacovigilance activities;

   (d) minimum requirements for the monitoring of data in the Eudravigilance database to determine whether there are new risks or whether risks have changed;

   (e) the format and content of the electronic transmission of suspected adverse reactions by Member States and the marketing authorisation holder;

   (f) the format and content of electronic periodic safety update reports and risk management plans;

   (g) the format of protocols, abstracts and final study reports for the post-authorisation safety studies.

2. Those measures shall take account of the work on international harmonisation carried out in the area of pharmacovigilance. Those measures shall be adopted in accordance with the regulatory procedure referred to in Article 214(2).

Article 123

Guidance to facilitate the performance of pharmacovigilance activities

The Agency shall, in cooperation with competent authorities of the Member States and other interested parties, draw up:

(a) guidance on good pharmacovigilance practices for both competent authorities and marketing authorisation holders;

(b) scientific guidance on post-authorisation efficacy studies.

Article 124

Reporting on pharmacovigilance tasks

The Agency shall make public a report on the performance of pharmacovigilance tasks by the Member States and the Agency every three years. The first report shall be made public by [three years after application date of [revised Regulation (EC) No 726/2004].

Chapter X
Homeopathic medicinal products and traditional herbal medicinal products

SECTION 1

SPECIFIC PROVISIONS APPLICABLE TO HOMEOPATHIC MEDICINAL PRODUCTS

Article 125

Registration or authorisation of homeopathic medicinal products

1. Member States shall ensure that homeopathic medicinal products manufactured and placed on the market in the Union are registered in accordance with Articles 126 and 127 or authorised in accordance with Article 133(1), except where such homeopathic medicinal products are covered by a registration or authorisation granted in accordance with national legislation on or before 31 December 1993. In case of registrations, Chapter III, Sections 3 and 4, and Article 38, paragraphs 1, 2 and 3 shall apply.

2. Member States shall establish a simplified registration procedure referred to in Article 126 for the homeopathic medicinal products.

Article 126

Simplified registration procedure for homeopathic medicinal products

1. Homeopathic medicinal products that satisfy all of the following conditions may be subject to a simplified registration procedure:

   (a) they are administered orally or externally;

   (b) no specific therapeutic indication appears on the labelling of the medicinal product or in any information relating thereto;

   (c) there is a sufficient degree of dilution to guarantee the safety of the medicinal product.

   For the purposes of point (c), the medicinal product may not contain either more than one part per 10000 of the mother tincture or more than 1/100th of the smallest dose used in allopathy with regard to active substances whose presence in an allopathic medicinal product results in the obligation to submit a doctor’s prescription.

   The Commission is empowered to adopt delegated acts in accordance with Article 215 to amend the first subparagph, point (c), in order to take account of scientific progress.

   At the time of registration, Member States shall determine the prescription status for the dispensing of the homeopathic medicinal product.

2. The criteria and rules of procedure provided for in Article 1(10), point (c), Article 30, Chapter III, Section 6, Articles 191, 195 and 204 shall apply by analogy to the simplified registration procedure for homeopathic medicinal products, with the exception of the proof of therapeutic efficacy.

Article 127

Application requirements for simplified registration

An application a simplified registration may cover a series of homeopathic medicinal products derived from the same homeopathic stock or stocks. The following shall be included with the application in order to demonstrate, in particular, the pharmaceutical quality and the batch-to-batch homogeneity of the homeopathic medicinal products concerned:

(a) the scientific name or other name given in a pharmacopoeia of the homeopathic stock or stocks, together with a statement of the various routes of administration, pharmaceutical forms and degree of dilution to be registered;

(b) a dossier describing how the homeopathic stock or stocks are obtained and controlled, and justifying their homeopathic use, on the basis of an adequate bibliography;

(c) the manufacturing and control file for each pharmaceutical form and a description of the method of dilution and potentisation;

(d) the manufacturing authorisation for the homeopathic medicinal product concerned;

(e) the copies of any registrations or authorisations obtained for the same homeopathic medicinal product in other Member States;

(f) one or more mock-ups of the outer packaging and the immediate packaging of the homeopathic medicinal products to be registered;

(g) the data concerning the stability of the homeopathic medicinal product.

Article 128

Application of decentralised and mutual recognition procedures to homeopathic medicinal products

1. Article 38, paragraphs 4 and 6, Articles 39 to 42 and 95 shall not apply to the homeopathic medicinal products referred to in Article 126.

2. Chapter III, Sections 3 to 5, shall not apply to the homeopathic medicinal products referred to in Article 133(2).

Article 129

Labelling of homeopathic medicinal products

Homeopathic medicinal products, with the exception those referred to in Article 126(1), shall be labelled in accordance with the provisions of Chapter VI and shall be identified by a reference on their labels, in clear and legible form, to their homeopathic nature.

Article 130

Specific requirements for labelling of certain homeopathic medicinal products

1. The labelling and, where appropriate, the package insert for homeopathic medicinal products referred to in Article 126(1) in addition to the clear mention of the words ‘homeopathic medicinal product’, shall bear the following, and no other, information:

   (a) the scientific name of the stock or stocks followed by the degree of dilution, making use of the symbols of the pharmacopoeia used in accordance with Article 4(62);

   (b) name and address of the registration holder and, where appropriate, of the manufacturer;

   (c) method of administration and, if necessary, route of administration;

   (d) pharmaceutical form;

   (e) expiry date, in clear terms (month, year);

   (f) contents of the sales presentation;

   (g) special storage precautions, if any;

   (h) a special warning if necessary for the medicinal product;

   (i) manufacturer's batch number;

   (j) registration number;

   (k) ‘homeopathic medicinal product without approved therapeutic indications’;

   (l) a warning advising the user to consult a doctor if the symptoms persist.

   As regards the first subparagraph, point (a), if the homeopathic medicinal product is composed of two or more stocks, the scientific names of the stocks on the labelling may be supplemented by an invented name.

2. Notwithstanding paragraph 1, Member States may require the use of certain types of labelling in order to show:

   (a) the price of the homeopathic medicinal product;

   (b) the conditions for refunds by social security bodies.

Article 131

Advertising of homeopathic medicinal products

1. Chapter XIII shall apply to homeopathic medicinal products.

2. By derogation from paragraph 1, Article 176(1) shall not apply to medicinal products referred to in Article 126(1).

   However, only the information specified in Article 130(1) may be used in the advertising of such homeopathic medicinal products.

Article 132

Exchange of information on homeopathic medicinal products

Member States shall communicate to each other all the information necessary to guarantee the quality and safety of homeopathic medicinal products manufactured and marketed within the Union, and in particular the information referred to in Articles 202 and 203.

Article 133

Other requirements for homeopathic medicinal products

1. Homeopathic medicinal products other than those referred to in Article 126(1) shall be granted a marketing authorisation in accordance with Articles 6 and 9 to 14 and labelled in accordance with Chapter VI.

2. A Member State may introduce or retain in its territory specific rules for the non-clinical tests and clinical studies of homeopathic medicinal products other than those referred to in Article 126(1), in accordance with the principles and characteristics of homeopathy as practised in that Member State.

   In this case, the Member State concerned shall notify the Commission of the specific rules in force.

3. Chapter IX shall apply to homeopathic medicinal products, with the exception of those referred to in Article 126(1). Chapter XI, Chapter XII, Section 1, and Chapter XIV shall apply to homeopathic medicinal products.

SECTION 2

SPECIFIC PROVISIONS APPLICABLE TO TRADITIONAL HERBAL MEDICINAL PRODUCTS

Article 134

Simplified registration procedure for traditional herbal medicinal products

1. Herbal medicinal products that satisfy all of the following conditions may be subject to a simplified registration procedure (‘traditional-use registration’):

   (a) they have therapeutic indications exclusively appropriate to traditional herbal medicinal products that, by virtue of their composition and purpose, are intended and designed for use without the supervision of a medical practitioner for diagnostic purposes or for prescription or monitoring of treatment;

   (b) they are exclusively for administration in accordance with a specified strength and posology;

   (c) they are an oral, external or inhalation preparation;

   (d) the period of traditional use as laid down in Article 136(1), point (c), has elapsed;

   (e) the data on the traditional use of the herbal medicinal product referred to in Article 136(1), point (c), are sufficient.

   The data on the use of a medicinal product referred to in the first subparagraph, point (e), shall be considered sufficient where the herbal medicinal product proves not to be harmful in the specified conditions of use and the pharmacological effects or efficacy of the herbal medicinal product are plausible on the basis of long-standing use and experience.

2. Notwithstanding Article 4(1), point (64), the presence in the herbal medicinal product of vitamins or minerals for the safety of which there is well-documented evidence shall not prevent the herbal medicinal product from being eligible for registration in accordance with paragraph 1, provided that the action of the vitamins

or minerals is ancillary to that of the herbal active substances regarding the specified claimed therapeutic indication(s).

3. However, in cases where the competent authorities judge that a herbal medicinal product that fulfils the conditions laid down in paragraph 1 (‘traditional herbal medicinal product’) fulfils the criteria for a national marketing authorisation in accordance with Article 5 or for a simplified registration in accordance with Article 126, the provisions of this Section shall not apply.

Article 135

Submission of dossier for traditional herbal medicinal product

1. The applicant and the traditional-use registration holder shall be established in the Union.

2. In order to obtain a traditional-use registration, the applicant shall submit an application to the competent authority of the Member State concerned.

Article 136

Application requirements for traditional-use registration

1. An application for traditional-use registration shall be accompanied by:

   (a) the particulars and documentation:

      (i) referred to in points (1), (2), (3), (5) to (9), (16) and (17) of Annex I;

      (ii) the results of the pharmaceutical tests referred to in Annex I;

      (iii) the summary of product characteristics, without the clinical particulars as specified in Annex V;

      (iv) in case of combinations, as referred to in Article 4(1), point (64), or in Article 134(2), the information referred to in Article 134(1), first subparagraph, point (e), relating to the combination as such; if the individual active substances are not sufficiently known, the data shall also relate to the individual active substances;

   (b) any national marketing authorisation or registration obtained by the applicant in another Member State, or in a third country, to place the herbal medicinal product on the market, and details of any decision to refuse to grant a national marketing authorisation or registration, whether in the Union or a third country, and the reasons for any such decision;

   (c) bibliographical or expert evidence to the effect that the herbal medicinal product in question, or a corresponding medicinal product has been in medicinal use throughout a period of at least 30 years preceding the date of the application, including at least 15 years within the Union;

   (d) a bibliographic review of safety data together with an expert report, and where required by the competent authority of the Member State, upon additional request, data necessary for assessing the safety of the herbal medicinal product.

   For the purposes of the first subparagraph, point (c), at the request of the Member State where the application for traditional-use registration has been submitted, the herbal medicinal products working group shall draw up an opinion on the adequacy

of the evidence of the long-standing use referred to in the first subparagraph, point (c), of the herbal medicinal product, or of the corresponding herbal medicinal product. The Member State shall submit relevant documentation supporting the referral.

For the purposes of the first subparagraph, point (d), if the individual active substances are not sufficiently known, the data referred to in the first subparagraph, point (a)(iv), shall also relate to the individual active substances.

Annex II shall apply by analogy to the particulars and documentations specified in the first subparagraph, point (a).

2. The requirement to show medicinal use throughout the period of at least 30 years, set out in paragraph 1, first subparagraph, point (c), is satisfied even where the marketing of the herbal medicinal product has not been based on a specific marketing authorisation. It is likewise satisfied where the number or quantity of ingredients of the herbal medicinal product has been reduced during that period.

3. Where the herbal medicinal product has been used in the Union for less than 15 years but is otherwise eligible for a traditional-use registration in accordance with paragraph 1, the competent authority of the Member State where the application for traditional-use registration has been submitted shall refer the application for the traditional herbal medicinal product to the herbal medicinal products working group and submit relevant documentation supporting this referral.

The herbal medicinal products working group shall consider whether the criteria other than the period of transitional use for a traditional-use registration as referred to in Article 134 are complied with. If the herbal medicinal products working group considers it possible, it shall establish a Union herbal monograph as referred to in Article 141(3) which shall be taken into account by the competent authority of Member State when taking its final decision on the application for the traditional use registration.

Article 137

Application of mutual recognition to traditional herbal medicinal products

1. Chapter III, Sections 3 to 5, shall apply by analogy to traditional-use registrations granted in accordance with Article 134, provided that:

   (a) a Union herbal monograph has been established in accordance with Article 141(3); or

   (b) the traditional herbal medicinal product consists of herbal substances, herbal preparations or combinations thereof contained in the list referred to in Article 139.

2. For traditional herbal medicinal products not covered by paragraph 1, the competent authority of each Member State shall, when evaluating an application for traditional-use registration, take due account of registrations granted by the competent authority of another Member State in accordance with this Section.

Article 138

Refusal of registration of traditional herbal medicinal products

1. Traditional-use registration shall be refused if the application does not comply with Articles 134, 135 or 136 or if at least one of the following conditions is fulfilled:

   (a) the qualitative or quantitative composition is not as declared;

   (b) the therapeutic indications do not comply with the conditions laid down in Article 134;

   (c) the traditional herbal medicinal product could be harmful under normal conditions of use;

   (d) the data on traditional use are insufficient, especially if pharmacological effects or efficacy are not plausible on the basis of long-standing use and experience;

   (e) the pharmaceutical quality is not satisfactorily demonstrated.

2. The competent authorities of the Member States shall notify the applicant, the Commission and any competent authority of the Member State that requests it, of any decision they take to refuse traditional-use registration and the reasons for the refusal.

Article 139

List of herbal substances, herbal preparations and combinations thereof

1. The Commission shall adopt implementing acts to establish a list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products, taking into account the draft list prepared by the herbal medicinal products working group. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 214(2). The list shall contain, with regard to each herbal substance, the therapeutic indication, the specified strength and the posology, the route of administration and any other information necessary for the safe use of the herbal substance as a traditional herbal medicinal product.

2. If an application for traditional-use registration relates to a herbal substance, preparation or a combination thereof contained in the list referred to in paragraph 1, the data specified in Article 136(1), points (b), (c) and (d), shall not be required and Article 138(1), points (c) and (d), shall not apply.

3. If a herbal substance, preparation or a combination is no longer included in the list referred to in paragraph 1, registrations pursuant to paragraph 2 for herbal medicinal products containing this substance shall be revoked unless the particulars and documentations referred to in Article 136(1) are submitted within three months.

Article 140

Other requirements for traditional herbal medicinal products

1. Article 1(5), points (a) and (b) and Article 1(10), point (c), Articles 6 to 8, 29, 30, 44, 46, 90, 155, Article 188, paragraphs 1 and 11, Articles 191, 195, 196, 198, 199(2), 202, 203 and 204 and Chapters IX and XI of this Directive as well as Commission

Directive 2003/94/EC[40] shall apply, *mutadis mutandis*, to traditional-use registrations granted under this Section.

2. In addition to the requirements set out in Articles 63 to 66, 70 to 79 and Annex IV, any labelling and package leaflet of a traditional herbal medicinal product shall contain a statement to the effect that:

   (a) the product is a traditional herbal medicinal product for use in specified therapeutic indication(s) exclusively based upon long-standing use; and

   (b) the user should consult a doctor or a qualified healthcare practitioner if the symptoms persist during the use of the traditional herbal medicinal product or if adverse effects not mentioned in the package leaflet occur.

   A Member State may require that the labelling and the package leaflet shall also state the nature of the tradition in question.

3. In addition to the requirements set out in Chapter XIII, any advertisement for a traditional herbal medicinal product registered under this Section shall contain the following statement: Traditional herbal medicinal product for use in specified therapeutic indication(s) exclusively based upon long-standing use.

Article 141

Herbal medicinal products working group

1. A herbal medicinal products working group is established as referred to in Article 142 of [revised Regulation (EC) No 726/2004]. That working group shall be part of the Agency and shall have the following competence:

   (a) as regards traditional-use registrations, to:

      (i) perform the tasks arising from Article 136, paragraphs 1 and 3;

      (ii) perform the tasks arising from Article 137;

      (iii) prepare a draft list of herbal substances, preparations and combinations thereof, as referred to in Article 139(1);

      (iv) establish Union monographs for traditional herbal medicinal products, as referred to in paragraph 3;

   (b) as regards marketing authorisations of herbal medicinal products, to establish Union herbal monographs for herbal medicinal products, as referred to in paragraph 3;

   (c) as regards referrals to the Agency under Chapter III, Section 5, or Article 95, in relation to traditional herbal medicinal products as referred to in Article 134, to perform the tasks set out in Article 41;

   (d) where a matter concerning medicinal products, other than the traditional-use medicinal products, other medicinal products containing herbal substances is referred to the Agency under Chapter III, Section 5, or Article 95, to give an opinion on the herbal substance, where appropriate.

[40] Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use (OJ L 262, 14.10.2003, p. 22).

Appropriate coordination with the Committee for Human Medicinal Products for Human Use shall be ensured by a procedure to be determined by the Executive Director of the Agency in accordance with Article 145(10) of [revised Regulation (EC) No 726/2004].

2. Each Member State shall appoint, for a three-year term which may be renewed, one member and one alternate to the herbal medicinal working group.

The alternates shall represent and vote for the members in their absence. Members and alternates shall be chosen for their role and experience in the evaluation of herbal medicinal products and shall represent the competent authorities of the Member States.

The members of the herbal medicinal products working group may be accompanied by experts in specific scientific or technical fields.

3. The herbal medicinal products working group shall establish Union herbal monographs for herbal medicinal products with regard to the application submitted in accordance with of Article 13 as well as traditional herbal medicinal products.

Where the Union herbal monographs have been established, they shall be taken into account by the competent authorities of Member States when examining an application. Where no such Union herbal monograph has yet been established, other appropriate monographs, publications or data may be referred to.

When new Union herbal monographs are established, the traditional-use registration holder shall consider whether it is necessary to modify the registration dossier accordingly. The traditional-use registration holder shall notify any such modification to the competent authority of the Member State concerned.

The herbal monographs shall be published.

4. Provisions of Article 146, paragraphs 3 to 5 of the [revised Regulation (EC) No 726/2004] applying to the working party shall apply by analogy to herbal medicinal products working group.

5. The herbal medicinal products working group shall draft its rules of procedure.

Chapter XI
Manufacturing and import

SECTION 1

MANUFACTURING AND IMPORT OF MEDICINAL PRODUCTS

Article 142

Manufacturing authorisation

1. Member States shall take all appropriate measures to ensure that the manufacture of the medicinal products within their territory is subject to authorisation (the "manufacturing authorisation"). The manufacturing authorisation shall be required also if the medicinal products manufactured are intended for export.

2. The manufacturing authorisation referred to in paragraph 1 shall be required for both total and partial manufacture, and for the various processes of dividing up, packaging or presentation.

3. By derogation from paragraph 2, the manufacturing authorisation shall not be required for the following:

   (a) preparation, dividing up, changes in packaging or presentation where these processes are carried out, solely for retail supply, by pharmacists in dispensing pharmacies or by persons legally authorised in the Member States to carry out such processes; or

   (b) decentralised sites carrying out manufacturing or testing steps under the responsibility of the qualified person of a central site referred to in Article 151(3).

4. A manufacturing authorisation shall also be required for imports of medicinal products coming from third countries into a Member State.

   This Chapter and Articles 195(5) and 198 shall apply to imports of medicinal products from third countries.

5. Member States shall enter the information relating to the manufacturing authorisation referred to in paragraph 1 in the Union database referred to in Article 188(15).

Article 143

Requirements for a manufacturing authorisation

1. In order to obtain the manufacturing authorisation, the applicant shall submit an application by electronic means to the competent authority of the Member State concerned.

   That application shall include the following particulars:

   (a) the medicinal products, the pharmaceutical forms and the manufacturing operations that are to be manufactured, imported or carried out and the place where the activity will take place;

   (b) proof that the applicants have at their disposal, for the manufacture or import of the above, suitable and sufficient premises, technical equipment and control facilities complying with the legal requirements that the Member State concerned lays down as regards both manufacture and control and the storage of medicinal products, in accordance with Article 8;

   (c) proof that the applicants have at their disposal the services of at least one qualified person within the meaning of Article 151;

   (d) explanation on whether the site is the central site responsible for the oversight of decentralised sites.

2. The applicant shall provide, by electronic means, particulars in support of the above in their application.

Article 144

Granting of a manufacturing authorisation

1. The official representatives of the competent authority of the Member State concerned shall carry out an inspection to ensure the accuracy of the particulars included in the application submitted in accordance with Article 143.

   Where the accuracy of the particulars is confirmed in accordance with the first subparagraph and no later than 90 days after the receipt of the application submitted in accordance with Article 143, the competent authority of the Member State shall grant or refuse a manufacturing authorisation.

2. To ensure that the particulars referred to in Article 143 are duly submitted, the competent authority of the Member State may grant a manufacturing authorisation subject to conditions.

   For central sites, a manufacturing authorisation shall include for each decentralised site a written confirmation that the manufacturer of the medicinal product has verified compliance of the decentralised site with principles of good manufacturing practice referred to in Article 160 by conducting regular audits in accordance with Article 147(1), first subparagraph, point (f).

3. The manufacturing authorisation shall apply only to the medicinal products, pharmaceutical forms, the manufacturing operations and the premises specified in the application and to the premises of the corresponding central site where decentralised manufacturing or testing activities are carried out in decentralised sites, which are registered in accordance with Article 148.

Article 145

Changes in a manufacturing authorisation

If the manufacturing authorisation holder requests a change in any of the particulars referred to in Article 143(1), second subparagraph, the competent authority of the Member State shall amend the manufacturing authorisation no later than 30 days from such request. In exceptional cases this period of time may be extended to 90 days.

Article 146

Request for additional information

The competent authority of the Member State may request the applicant to submit additional information on the particulars supplied pursuant to Article 143(1) and on the qualified person referred to in Article 151; where the competent authority of the Member State makes such request, the time limits referred to in Articles 144(1), second subparagraph, and 145 shall be suspended until the additional information has been supplied.

Article 147

Obligations of the manufacturing authorisation holder

1. Member States shall ensure that manufacturing authorisation holders shall:

   (a) have at their disposal the services of staff who comply with the legal requirements existing in the Member State both as regards manufacture and controls;

   (b) dispose of the medicinal products that have been granted a marketing authorisation only in accordance with the legislation of the Member States;

(c) give prior notice to the competent authority of the Member State of any changes they may wish to make to any of the particulars provided in accordance to Article 143;

(d) allow the official representatives of the competent authority of the Member State access to their premises and, where sites carry out manufacturing or testing activities in connection with a central site in the decentralised site, to the premises of the central or the decentralised sites at any time;

(e) enable the qualified persons referred to in Article 151 to carry out their duties, where appropriate also in decentralised sites, for example by placing at their disposal all the necessary resources;

(f) comply, in any relevant site and at all times with the principles of good manufacturing practice for medicinal products;

(g) use only active substances that have been manufactured in accordance with good manufacturing practice for active substances and distributed in accordance with good distribution practices for active substances;

(h) inform the competent authority of the Member State and the marketing authorisation holder immediately if they obtain information that medicinal products that come under the scope of their manufacturing authorisation are, or are suspected of being, falsified irrespective of the way the medicinal products were distributed;

(i) verify that the manufacturers, importers or distributors from whom they obtain active substances are registered with the competent authority of the Member State in which they are established; and

(j) verify the authenticity and quality of the active substances and the excipients.

As regards the first subparagraph, point (c), the competent authority of the Member State shall, in any event, be immediately informed if the qualified person referred to in Articles 143(1), point (c), and 151 is replaced unexpectedly.

For the purposes of points (f) and (g), manufacturing authorisation holders shall verify compliance, respectively, by the manufacturer or distributors of active substances with good manufacturing practice and good distribution practices by conducting audits at the manufacturing and distribution sites of the manufacturer and distributors of active substances. Manufacturing authorisation holders shall verify such compliance either by themselves or through an entity acting on their behalf under a contract.

2. The manufacturing authorisation holder shall ensure that the excipients are suitable for use in medicinal products by ascertaining the appropriate good manufacturing practice on the basis of a formalised risk assessment.

3. The manufacturing authorisation holder shall ensure that the appropriate good manufacturing practice ascertained in accordance with paragraph 2, is applied. The manufacturing authorisation holder shall document the measures taken in accordance with paragraphs 1 and 2.

Article 148

Registration and listing process of decentralised sites

1. The manufacturing authorisation holder of the central site shall register all of its decentralised sites in accordance with the provisions of this Article.

2. The manufacturing authorisation holder of the central site shall request the competent authority of the Member State in which the decentralised site is established, to register the decentralised site.

3. The marketing authorisation holder may commence the activity in the decentralised site in connection with the central site only when the decentralised site is registered in the Union database referred to in Article 188(15) and the link is made in the database with the authorisation of the corresponding central site by the competent authority of the Member state where the decentralised site is located.

4. The competent authority of the Member State in which the decentralised site is established, is responsible, in accordance with Article 188, for the supervision of the manufacturing and testing activities carried out in the decentralised site.

5. For the purpose of paragraph 2 the manufacturing authorisation holder of the central site shall submit a registration form that shall include, at least, the following information:

   (a) name or corporate name and permanent address of the decentralised site and a proof of establishment in the Union;

   (b) the medicinal products that are subject to manufacturing or testing steps in the decentralised site, including the manufacturing or testing activities to be performed for those medicinal products;

   (c) particulars regarding the premises of the decentralised site and the technical equipment to carry out the relevant activities;

   (d) the reference to the manufacturing authorisation of the central site;

   (e) the written confirmation referred to in Article 144(2), second subparagraph, that the manufacturer of the medicinal product has verified compliance of the decentralised site with principles of good manufacturing practice referred to in Article 160 by conducting audits.

6. The competent authority of the Member State supervising the decentralised site pursuant to paragraph 4 may decide to carry out an inspection as referred to in Article 188(1), first subparagraph, point (a). In such cases, that competent authority shall cooperate with the competent authority of the Member State responsible for the supervision of the central site.

7. Following the registration of the decentralised site pursuant to paragraph 2, the manufacturing authorisation holder of the central site shall list the registered decentralised site in the manufacturing authorisation of the central site.

8. The competent authority of the Member State supervising the decentralised site pursuant to paragraph 4 shall cooperate with the relevant authorities responsible for the supervision of the manufacturing or testing activities under other Union acts as regards the following:

   (a) the medicinal products that were manufactured in a decentralised site, the testing or manufacturing of which involves using raw material, medicinal products regulated under other relevant Union law, or medicinal products that are intended to be combined with medical devices;

(b) where specific manufacturing or testing activities are applied to the medicinal products containing, consisting or derived from SoHO for which specific manufacturing or testing activities are applied within a decentralised site that is also authorised under [SoHO Regulation].

9. Where relevant, competent authorities of the Member State supervising the central and decentralised sites may liaise with the competent authority of the Member State responsible for the supervision of the marketing authorisation.

Article 149

Conditions related to the safety feature

1. The safety features referred to in Annex IV shall not be removed or covered, either fully or partially, unless the following conditions are fulfilled:

(a) the manufacturing authorisation holder verifies, prior to partly or fully removing or covering those safety features, that the medicinal product concerned is authentic and that it has not been tampered with;

(b) the manufacturing authorisation holder complies with Annex IV by replacing those safety features with safety features that are equivalent as regards the possibility to verify the authenticity, identification and to provide evidence of tampering of the medicinal product. Such replacement shall be conducted without opening the immediate packaging.

Safety features shall be considered equivalent if they:

(i) comply with the requirements set out in the delegated acts adopted pursuant to Article 67(2); and

(ii) are equally effective in enabling the verification of authenticity and identification of medicinal products and in providing evidence of tampering with medicinal products;

(c) the replacement of the safety features is conducted in accordance with applicable good manufacturing practice for medicinal products; and

(d) the replacement of the safety features is subject to supervision by the competent authority of the Member State.

2. Manufacturing authorisation holders, including those performing the activities referred to in paragraph 1, shall be regarded as producers and therefore held liable for damages in the cases and under the conditions set forth in Directive 85/374/EEC.

Article 150

Potentially falsified medicinal products

1. By derogation from Article 1(2), and without prejudice to Chapter XII, Section 1, Member States shall take the necessary measures in order to prevent medicinal products that are introduced into the Union, but are not intended to be placed on the market in the Union, from entering into circulation if there are sufficient grounds to suspect that those products are falsified.

2. Member States shall organise meetings involving patients' and consumers' organisations and, as necessary, Member States' enforcement officers, in order to

communicate public information about the actions undertaken in the area of prevention and enforcement to combat the falsification of medicinal products.

3. In order to establish what the necessary measures referred to in paragraph 1 are the Commission is empowered to adopt delegated acts in accordance with Article 215, to supplement paragraph 1 by specifying the criteria to be considered and the verifications to be made when assessing the potential falsified character of medicinal products introduced into the Union but not intended to be placed on the market.

Article 151

Availability of qualified person

1. Member States shall take all appropriate measures to ensure that the manufacturing authorisation holder has permanently and continuously at their disposal the services of at least one qualified person residing and operating in the Union, in accordance with the conditions laid down in Article 152, responsible in particular for carrying out the duties specified in Article 153.

2. A manufacturing authorisation holder who is a natural person and personally fulfils the conditions laid down in Annex III may assume the responsibility referred to in paragraph 1.

3. Where the manufacturing authorisation is granted to a central site specified in the application pursuant to Article 144(3), the qualified person referred to in paragraph 1 shall also be responsible for carrying out the duties specified in Article 153(4) regarding the decentralised sites.

Article 152

Qualification of qualified person

1. Member States shall ensure that the qualified person referred to in Article 151 fulfils the conditions of qualification set out in Annex III.

2. The manufacturing authorisation holder and the qualified person shall ensure that the practical experience acquired is appropriate to the types of products to be certified.

3. The competent authority of the Member State may lay down appropriate administrative procedures to verify that a qualified person referred to in the paragraph 1 fulfils the conditions set out in Annex III.

Article 153

Responsibilities of the qualified person

1. Member States shall take all appropriate measures to ensure that the qualified person referred to in Article 151, without prejudice to their relationship with the manufacturing authorisation holder, are responsible, subject to the procedures referred to in Article 154, for securing:

   (a) in the case of medicinal products manufactured within the Member States concerned, that each production batch of medicinal products has been manufactured and checked in compliance with the laws in force in that Member State and in accordance with the requirements of the marketing authorisation;

(b) in the case of medicinal products imported from third countries, irrespective of whether they have been manufactured in the Union that each production batch has undergone in a Member State a full qualitative analysis, a quantitative analysis of at least all the active substances and all the other tests or checks necessary to ensure the quality of the medicinal products in accordance with the requirements of the marketing authorisation.

The qualified person referred to in Article 151 shall in the case of medicinal products intended to be placed on the Union market, ensure that the safety features referred to in Annex IV have been affixed on the packaging.

The batches of medicinal products that have undergone the controls referred to in the first subparagraph, point (b), in a Member State shall be exempt from those controls if they are marketed in another Member State, accompanied by the control reports signed by the qualified person.

2. In the case of medicinal products imported from a third country, where appropriate arrangements have been made by the Union with the exporting country to ensure that the manufacturer applies standards of good manufacturing practice at least equivalent to those laid down by the Union, and to ensure that the controls referred to in paragraph 1, first subparagraph, point (b), have been carried out in the exporting country, the qualified person may be relieved of responsibility for carrying out those controls.

3. In all cases and particularly where the medicinal products are released for sale, the qualified person shall certify in a register or equivalent format provided for that purpose, that each production batch satisfies the provisions of this Article; that register or equivalent format shall be kept up to date during the time when operations are carried out and shall remain at the disposal of the official representatives of the competent authority of the Member State for the period specified in the provisions of the Member State concerned and in any event for at least five years.

4. For the purposes of Article 151(3), the qualified person shall, in addition:

(a) supervise that the manufacturing or testing activities carried out at the decentralised sites comply with principles of relevant good manufacturing practices referred to in Article 160 and conform to the marketing authorisation;

(b) provide a written confirmation as referred to in Article 144(2), second subparagraph;

(c) notify to the competent authority of the Member State where the decentralised site is established, an inventory of the changes that have taken place as regards the information provided in the registration form submitted pursuant to Article 148(5).

Any changes that may have an impact on the quality or safety of the medicinal products that are manufactured or tested at the decentralised site must be notified immediately.

The Commission is empowered to adopt a delegated act in accordance with Article 215 to supplement the first subparagraph, point (c), specifying the notification made by the qualified person.

Article 154

Professional code of conduct

1. Member States shall ensure that the duties of qualified persons referred to in Article 151 are fulfilled, either by means of appropriate administrative measures or by making such persons subject to a professional code of conduct.

2. Member States may provide for the temporary suspension of a qualified person referred to in Article 151 upon the commencement of administrative or disciplinary procedures against that qualified person for failure to fulfil its duties set out in Article 153.

Article 155

Certificate for export of a medicinal product

1. At the request of the manufacturer, the exporter or the competent authorities of an importing third country, Member States shall certify that a manufacturer of medicinal products is in possession of a manufacturing authorisation. When issuing such certificates Member States shall:

   (a) comply with the prevailing administrative arrangements of the World Health Organization;

   (b) for medicinal products intended for export that are already authorised in their territory, supply the summary of product characteristics as approved by them in accordance with Article 43.

2. When the manufacturer is not in possession of a marketing authorisation it shall provide the competent authorities responsible for issuing the certificate referred to in paragraph 1, with a declaration explaining why a marketing authorisation is not available.

SECTION 2

MANUFACTURING, IMPORT AND DISTRIBUTION OF ACTIVE SUBSTANCES

Article 156

Manufacture of active substances

For the purposes of this Directive, manufacture of active substances used in the manufacturing process of a medicinal product shall include both total and partial manufacture or import of an active substance and the various processes of dividing up, packaging or presentation prior to its incorporation into a medicinal product, including repackaging or re-labelling, such as are carried out by a distributor of active substances.

Article 157

Registration of importers, manufacturers and distributors of active substances

1. Importers, manufacturers and distributors of active substances who are established in the Union shall register their activity with the competent authority of the Member State in which they are established.

2. The registration form, to be submitted by electronic means, shall include, at least, the following information:

(a) name or corporate name and permanent address;

(b) the active substances that are to be imported, manufactured or distributed;

(c) particulars regarding the premises and the technical equipment for their activity.

3. The persons referred to in paragraph 1 shall submit, by electronic means, the registration form to the competent authority of the Member State at least 60 days prior to the intended commencement of their activity.

4. The competent authority of the Member State may, based on a risk assessment, decide to carry out an inspection. If the competent authority of the Member State notifies the applicant within 60 days of the receipt of the registration form that an inspection will be carried out, the activity shall not begin before the competent authority of the Member State has notified the applicant that they may commence the activity. If within 60 days of the receipt of the registration form the competent authority of the Member State has not notified the applicant that an inspection will be carried out, the applicant may commence the activity.

5. Annually, the persons referred to in paragraph 1 shall communicate, by electronic means, to the competent authority of the Member State an inventory of the changes that have taken place as regards the information provided in the registration form. Any changes that may have an impact on the quality or safety of the active substances that are manufactured, imported or distributed must be notified immediately.

6. The comptetent authority of the Member State shall enter the information provided in accordance with paragraph 2 in the Union database referred to in Article 188(15).

Article 158

Conditions for importing active substances

1. Member States shall take appropriate measures to ensure that the manufacture, import and distribution on their territory of active substances, including active substances that are intended for export, comply with the principles of good manufacturing practice and good distribution practices for active substances specified in the delegated acts adopted in accordance with Article 160.

2. Active substances shall only be imported if the following conditions are fulfilled:

(a) the active substances have been manufactured in accordance with the principles of good manufacturing practices at least equivalent to those laid down by the Union pursuant to Article160; and

(b) the active substances are accompanied by a written confirmation issued by the competent authority of the exporting third country stating that:

(i) the principles of good manufacturing practices applicable to the manufacturing site manufacturing the exported active substance are at least equivalent to those laid down by the Union pursuant Article 160;

(ii) the manufacturing site concerned is subject to regular, strict and transparent controls and to the effective enforcement of good

manufacturing practice, including repeated and unannounced inspections, so as to ensure a protection of public health at least equivalent to that in the Union; and

(iii) in the event of findings relating to non-compliance, information on such findings is supplied by the exporting third country to the Union without undue delay.

3. The conditions set out in paragraph 2, point (b), shall not apply if the exporting country is included in the list referred to in Article 159(2).

4. The conditions set out in paragraph 2, point (b), may be waived by any competent authority of a Member State for a period not exceeding the validity of the certificate of good manufacturing practice issued in accordance with Article 188(13) where a site manufacturing an active substance for export has been inspected by the competent authority of a Member State and was found to comply with the principles of good manufacturing practice laid down pursuant to Article160.

Article 159

Active substances imported from third countries

1. At the request of a third country, the Commission shall assess whether that country's regulatory framework applicable to active substances exported to the Union and the respective control and enforcement activities ensure a level of protection of public health equivalent to that of the Union.

The assessment shall take the form of a review of relevant documentation submitted by electronic means and, unless arrangements as referred to in Article 153(2) are in place that cover this area of activity, that assessment shall include an on-site review of the third country's regulatory system and, if necessary, an observed inspection of one or more of the third country's manufacturing sites for active substances.

2. Based on the assessment referred to in paragraph 1, the Commission may adopt implementing acts to include the third country in a list and to apply the requirements set out in the second subparagraph. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 214(2).

When assessing the third country pursuant to paragraph 1, the Commission shall take account of the following:

(a) the country's rules for good manufacturing practice;

(b) the regularity of inspections to verify compliance with good manufacturing practice;

(c) the effectiveness of enforcement of good manufacturing practice;

(d) the regularity and rapidity of information provided by the third country relating to non-compliant manufacturers of active substances.

3. The Commission shall verify regularly whether the conditions laid down in paragraph 1 are fulfilled. The first verification shall take place no later than 3 years after the third country has been included in the list referred to in paragraph 2.

4. The Commission shall perform the assessment referred to in pargarph 1 and verification referred to in paragraph 3 in cooperation with the Agency and the competent authorities of the Member States.

SECTION 3

PRINCIPLES OF GOOD MANUFACTURING AND GOOD DISTRIBUTION PRACTICES

Article 160

Rules applicable to medicinal products and active substances

The Commission may adopt implementing acts in accordance with Article 214(2) to supplement this Directive by specifying:

(a) the principles of good manufacturing and good distribution practices for medicinal products complemented, where relevant, by specific measures applicable notably to pharmaceutical forms, medicinal products or manufacturing activities in line with good manufacturing principles;

(b) the principles of good manufacturing and good distribution practices for active substances.

Where relevant, these principles shall be specified in coherence with any principles of good practices established under any other Union legal framework.

Article 161

Rules applicable to excipients

The Commission is empowered to adopt delegated acts in accordance with Article 215 to supplement this Directive on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients referred to in Article 147(2). Such risk assessment shall take into account requirements under other appropriate quality systems as well as the source and intended use of the excipients and previous instances of quality defects.

Chapter XII
Wholesale distribution and sale at a distance

SECTION 1

WHOLESALE DISTRIBUTION AND BROKERING OF MEDICINAL PRODUCTS

Article 162

Wholesale distribution of medicinal products

1. Without prejudice to Article 5, Member States shall take all appropriate action to ensure that only medicinal products in respect of which a marketing authorisation has been granted in accordance with Union law are distributed on their territory.

2. In the case of wholesale distribution including storage, medicinal products shall be covered by either a centralised marketing authorisation or by a national marketing authorisation.

3. Distributors who intend to import a medicinal product from another Member State shall notify the marketing authorisation holder and the competent authority of the

Member State to which the medicinal product is to be imported of their intention to import that medicinal product.

4. In the case of medicinal products covered by a national marketing authorisation, the notification referred to in paragraph 3 to the competent authority of the Member State shall be without prejudice to additional procedures provided for in the legislation of that Member State and to fees payable to the competent authority of the Member State for examining the notification.

5. In the case of medicinal products covered by a centralised marketing authorisation, the distributor shall submit the same notification referred to in paragraph 3 to the Agency which will be in charge of checking that the conditions laid down in Union law on medicinal products and in the marketing authorisations are observed. For this check, a fee shall be payable to the Agency.

Article 163

Authorisation for wholesale distribution of medicinal products

1. The competent authority of the Member State concerned shall take all appropriate measures to ensure that the wholesale distribution of medicinal products is subject to an authorisation to engage in activity as a wholesaler in medicinal products ("wholesale distribution authorisation"). The wholesale distribution authorisation shall indicate the premises, the medicinal products and the wholesale distribution operations for which it is valid.

2. Where persons authorised or entitled to supply medicinal products to the public may also, under national law, engage in wholesale business, such persons shall be subject to the authorisation provided for in paragraph 1.

3. A manufacturing authorisation required under Article 142 shall include an authorisation to distribute by wholesale the medicinal products that it covers. A wholesale distribution authorisation shall not give dispensation from the obligation set out in Article 142 to hold a manufacturing authorisation and to comply with the conditions set out in that respect, even where the manufacturing or import business is secondary.

4. The competent authority of the Member State concerned shall enter the information relating to the wholesale distribution authorisations in the Union database referred to in Article 188(15).

5. The competent authority of the Member State that granted the wholesale distribution authorisation for premises located in its territory shall ensure that controls of the persons authorised to engage in activity as a wholesaler in medicinal products, and inspections of their premises, are carried out at an appropriate frequency.

The competent authority of the Member State that granted the wholesale distribution authorisation shall suspend or revoke it if the conditions for granting it set out in Article 162 cease to be met. In such event the Member State shall without undue delay inform the other Member States and the Commission thereof.

6. Where a competent authority of a Member State considers that the conditions for granting a wholesale distribution authorisation set out in Article 162 are not met with respect to a wholesale distribution authorisation granted by the competent authority of another Member State, it shall without undue delay inform the Commission and the competent authority of the other Member State thereof. The competent authority

of the other Member State shall take the measures it considers necessary and shall inform the Commission and the competent authority of the first Member State of those measures and the reasons for them.

Article 164

Requirements for a wholesale distribution authorisation

1. In order to obtain a wholesale distribution authorisation, applicants shall submit an application by electronic means to the competent authority of the Member State concerned.

2. The application referred to in paragraph 1 shall include the following particulars:

   (a) a confirmation and proof that the applicants have at their disposal suitable and adequate premises, installations and equipment, to ensure proper conservation and distribution of the medicinal products;

   (b) a confirmation and proof that the applicants have at their disposal appropriately trained staff, and in particular, a qualified person designated as responsible, meeting the conditions provided for by the legislation of the Member State concerned;

   (c) an undertaking to fulfil the obligations incumbent on them under the terms of Article 166.

Article 165

Granting of a wholesale distribution authorisation

1. The official representatives of the competent authority of the Member State concerned shall carry out an inspection to confirm the accuracy of the particulars provided in accordance with Article 164.

   Where the accuracy of the particulars is confirmed in accordance with the first subparagraph and no later than 90 days after the receipt of the application submitted in accordance with Article164, the competent authority of the Member State shall grant or refuse a wholesale distribution authorisation.

2. The competent authority of the Member State concerned may require the applicant to supply, by electronic means, all necessary information concerning the particulars for granting the wholesale distribution authorisation. In such case, the period laid down in paragraph 1 shall be suspended until the requisite additional information is supplied.

3. The competent authority of the Member State may grant a wholesale distribution authorisation subject to conditions.

4. The wholesale distribution authorisation shall apply only to the premises specified in the authorisation.

Article 166

Obligations of the wholesale distribution authorisation holder

1. Member States shall ensure that wholesale distribution authorisation holders shall:

(a) have at their disposal the services of staff who comply with the legal requirements existing in the Member State as regards wholesale distribution;

(b) allow the official representatives of the competent authority of the Member State access to their premises, installations and equipment referred to in Article 164(2), point (a), at all times;

(c) obtain, including by financial transactions, their supplies of medicinal products only from persons who are themselves in possession of a wholesale distribution authorisation in the Union or a manufacturing authorisation referred to in Article 163(3);

(d) supply, including by financial transaction, medicinal products only to persons who are themselves wholesale distribution authorisation holders or who are authorised or entitled to supply medicinal products to the public;

(e) verify that the medicinal products received are not falsified by checking the safety features on the outer packaging, in accordance with the requirements laid down in the delegated acts adopted pursuant to Article 67(2), second subparagraph;

(f) have an emergency plan that ensures effective implementation of any recall from the market ordered by the competent authorities or carried out in cooperation with the manufacturer or marketing authorisation holder for the medicinal product concerned;

(g) keep records giving, for any medicinal products received, dispatched or brokered, at least the following information:

(i) the date of receipt, dispatch or brokering of the medicinal product,

(ii) the name of the medicinal product,

(iii) the quantity of the medicinal product received, supplied or brokered,

(iv) the name and address of the supplier of the medicinal product or the consignee, as appropriate,

(v) the batch number of the medicinal products, at least for medicinal products bearing the safety features referred to in Article 67;

(h) keep the records referred to in point (g) available to the competent authorities of the Member States, for inspection purposes, for a period of five years;

(i) comply with the principles of good distribution practices for medicinal products laid down in Article 160;

(j) maintain a quality system setting out responsibilities, processes and risk management measures in relation to their activities;

(k) immediately inform the competent authority of the Member State and, where applicable, the marketing authorisation holder, of medicinal products they receive or are offered that they identify as falsified or suspect to be falsified;

(l) continuously guarantee the appropriate and continued supply of an adequate range of medicinal products to meet the requirements of a specific geographical area, and deliver the supplies requested over the whole of the area in question, within a reasonable timeframe, which shall be defined in the national legislation;

(m) cooperate with marketing authorisation holders and competent authorities of the Member States on the security of supply.

2. Where the medicinal product is obtained from another wholesale distributor, the wholesale distribution authorisation holders obtaining the product shall verify compliance with the principles of good distribution practices by the supplying wholesale distributor. This includes verifying whether the supplying wholesale distributor holds a wholesale distribution authorisation, or a manufacturing authorisation referred to in Article 163(3).

3. Where the medicinal product is obtained from a manufacturer or importer, wholesale distribution authorisation holders shall verify that the manufacturer or importer holds a manufacturing authorisation.

4. Where the medicinal product is obtained through brokering of medicinal products, wholesale distribution authorisation holders shall verify that the person brokering the medicinal product fulfils the requirements set out in Article 171.

Article 167

Obligation of supply of medicinal products

1. With regard to the supply of medicinal products to pharmacists and persons authorised or entitled to supply medicinal products to the public, Member States shall not impose upon the wholesale distribution authorisation holder that has been granted by another Member State any obligation, in particular public service obligations, more stringent than those they impose on persons whom they have themselves authorised to engage in equivalent activities.

2. The wholesale distributors of a medicinal product placed on the market in a Member State shall, within the limits of their responsibilities, ensure appropriate and continued supplies of that medicinal product to pharmacies and persons authorised to supply medicinal products so that the needs of patients in the Member State in question are covered.

3. The arrangements for implementing this Article should, moreover, be justified on grounds of public health protection and be proportionate in relation to the objective of such protection, in compliance with the Treaty rules, particularly those concerning the free movement of goods and competition.

Article 168

Documentation accompanying supplied medicinal products

1. For all supplies of medicinal products to a person authorised or entitled to supply medicinal products to the public in the Member State concerned, the authorised wholesaler must enclose a document that makes it possible to ascertain the following:

(a) the date of the supply;

(b) the name and pharmaceutical form of the medicinal product;

(c) the quantity of the medicinal product supplied;

(d) the name and address of the supplier of the medicinal product and consignee;

(e) the batch number of the medicinal products at least for products bearing the safety features referred to in Article 67.

2. Member States shall take all appropriate measures to ensure that persons authorised or entitled to supply medicinal products to the public are able to provide information that makes it possible to trace the distribution path of every medicinal product.

Article 169

National requirements on wholesale distribution

The provisions of this Chapter shall not prevent the application of more stringent requirements laid down by Member States in respect of the wholesale distribution of:

(a) narcotic or psychotropic substances;

(b) medicinal products derived from blood;

(c) immunological medicinal products; and

(d) radiopharmaceuticals.

Article 170

Wholesale distribution to third countries

In the case of wholesale distribution of medicinal products to third countries, Articles 162 and 166(1), point (c), shall not apply.

Where wholesale distributors supply medicinal products to persons in third countries, they shall ensure that such supplies are only made to persons who are authorised or entitled to receive medicinal products for wholesale distribution or supply to the public in accordance with the applicable legal and administrative provisions of the third country concerned.

Article 168 shall apply to the supply of medicinal products to persons in third countries authorised or entitled to supply medicinal products to the public.

Article 171

Brokering medicinal products

1. Persons brokering medicinal products shall ensure that the brokered medicinal products are covered by a valid marketing authorisation.

   Persons brokering medicinal products shall have a permanent address and contact details in the Union, so as to ensure accurate identification, location, communication and supervision of their activities by competent authorities of the Member States.

   The requirements set out in Article 166(1), points (e) to (j), shall apply *mutatis mutandis* to the brokering of medicinal products.

2. Persons may only broker medicinal products if they are registered with the competent authority of the Member State where they have their permanent address referred to in paragraph 1, second subparagraph. Those persons shall submit, by electronic means, at least, their name, corporate name and permanent address to the competent authority in order to register. They shall notify, by electronic means, the competent authority of the Member State of any changes thereof without delay.

The competent authority of the Member State shall enter the information referred to in the first subparagraph in a register that shall be publicly available.

3. The principles referred to in Article 160 shall include specific provisions for brokering.

4. Inspections referred to in Article 188 shall be carried out under the responsibility of the Member State where the person brokering medicinal products is registered.

If a person brokering medicinal products does not comply with the requirements set out in this Article, the competent authority of the Member State may decide to remove that person from the register referred to in paragraph 2. In such event, the competent authority of the Member State shall notify that person thereof.

SECTION 2

SALE AT A DISTANCE TO THE PUBLIC

Article 172

General requirements for sale at distance

1. Without prejudice to national legislation prohibiting the offer for sale at a distance of prescription medicinal products to the public by means of information society services, Member States shall ensure that medicinal products are offered for sale at a distance to the public by means of services as defined in Directive (EU) 2015/1535 of the European Parliament and of the Council[41] laying down a procedure for the provision of information in the field of technical regulations and of rules on Information Society services under the following conditions:

(a) the natural or legal person offering the medicinal products is authorised or entitled to supply medicinal products to the public, also at a distance, in accordance with national legislation of the Member State in which that person is established;

(b) the person referred to in point (a) has notified the Member State in which that person is established of at least the following information:

(i) name or corporate name and permanent address of the place of activity from where those medicinal products are supplied;

(ii) the starting date of the activity of offering medicinal products for sale at a distance to the public by means of information society services;

(iii) the address of the website used for that purpose and all relevant information necessary to identify that website;

(iv) if applicable, the prescription status in accordance with Chapter IV of the medicinal products offered for sale at a distance to the public by means of information society services.

Where appropriate, that information shall be updated;

[41] Directive (EU) 2015/1535 of the European Parliament and of the Council of 9 September 2015 laying down a procedure for the provision of information in the field of technical regulations and of rules on Information Society services (OJ L 241, 17.9.2015, p. 1).

(c) the medicinal products comply with the national legislation of the Member State of destination in accordance with Article 5(1);

(d) without prejudice to the information requirements set out in Directive 2000/31/EC of the European Parliament and of the Council[42], the website offering the medicinal products contains at least:

(i) the contact details of the competent authority of the Member State or the authority notified pursuant to point (b);

(ii) a hyperlink to the website referred to in Article 174 of the Member State of establishment;

(iii) the common logo referred to in Article 173 clearly displayed on every page of the website that relates to the offer for sale at a distance to the public of medicinal products. The common logo shall contain a hyperlink to the entry of the person in the list referred to in Article 174(1), point (c).

2. Member States may impose conditions, justified on grounds of public health protection, for the retail supply on their territory of medicinal products for sale at a distance to the public by means of information society services.

3. Without prejudice to Directive 2000/31/EC and the requirements set out in this Section, Member States shall take the necessary measures to ensure that other persons than those referred to in paragraph 1 that offer medicinal products for sale at a distance to the public by means of information society services and that operate on their territory are subject to effective, proportionate and dissuasive penalties.

Article 173

Requirements for common logo

1. A common logo shall be established that is recognisable throughout the Union, while enabling the identification of the Member State where the person offering medicinal products for sale at a distance to the public is established. That logo shall be clearly displayed on websites offering medicinal products for sale at a distance to the public in accordance with Article 172(1), point (d).

2. In order to harmonise the functioning of the common logo, the Commission shall adopt implementing acts regarding:

(a) the technical, electronic and cryptographic requirements for verification of the authenticity of the common logo;

(b) the design of the common logo.

Those implementing acts shall, where necessary, be amended to take account of technical and scientific progress. Those implementing acts shall be adopted in accordance with the procedure referred to in Article 214(2).

[42] Directive 2000/31/EC of the European Parliament and of the Council of 8 June 2000 on certain legal aspects of information society services, in particular electronic commerce, in the Internal Market (Directive on electronic commerce (OJ L 178, 17.7.2000, p. 1).

Article 174

Information about the supply at distance to the public

1. Each Member State shall set up a website providing at least the following:

   (a) information on the national legislation applicable to the offering of medicinal products for sale at a distance to the public by means of information society services, including information on the fact that there may be differences between Member States regarding classification of medicinal products and the conditions for their supply;

   (b) information on the purpose of the common logo;

   (c) the list of persons offering the medicinal products for sale at a distance to the public by means of information society services in accordance with Article 172 as well as their website addresses;

   (d) background information on the risks related to medicinal products supplied illegally to the public by means of information society services.

   This website shall contain a hyperlink to the website referred to in paragraph 2.

2. The Agency shall set up a website providing the information referred to in paragraph 1, first subparagraph, points (b) and (d), information on the Union law applicable to falsified medicinal products as well as hyperlinks to the websites of the Member States referred to in paragraph 1. The Agency's website shall explicitly mention that the Member States' websites contain information on persons authorised or entitled to supply medicinal products by sales at a distance in the Member State concerned.

3. The Commission shall, in cooperation with the competent authorities, conduct or promote information campaigns aimed at the general public on the dangers of falsified medicinal products. Those campaigns shall raise consumer awareness of the risks related to medicinal products supplied illegally by sales at a distance as well as of the functioning of the common logo and the websites referred to in paragraphs 1 and 2.

Chapter XIII
Advertising

Article 175

Definition of advertising of medicinal products

1. For the purposes of this Chapter, 'advertising of medicinal products' shall include any form of door-to-door information, canvassing activity or inducement designed to promote the prescription, supply, sale or consumption of medicinal products.

   It shall include in particular:

   (a) the advertising of medicinal products to the general public;

   (b) advertising of medicinal products to persons qualified to prescribe, administer or supply them;

   (c) visits by medical sales representatives to persons qualified to prescribe medicinal products;

   (d) the supply of samples of medicinal products;

(e) the provision of inducements to prescribe or supply medicinal products by the gift, offer or promise of any benefit or bonus, whether in money or in kind, except when their intrinsic value is minimal;

(f) sponsorship of promotional meetings attended by persons qualified to prescribe or supply medicinal products;

(g) sponsorship of scientific congresses attended by persons qualified to prescribe or supply medicinal products and in particular payment of their travelling and accommodation expenses in connection therewith;

(h) advertising related to medicinal products, that does not refer to specific medicinal products.

2. The following are not covered by this Chapter:

(a) the labelling and package leaflets, which are subject to the provisions of Chapter VI;

(b) correspondence, possibly accompanied by material of a non-promotional nature, needed to answer a specific question about a particular medicinal product;

(c) factual, informative announcements and reference material relating, for example, to pack changes, adverse-reaction warnings as part of general drug precautions, trade catalogues and price lists, provided they include no product claims;

(d) information relating to human health or diseases, provided that there is no reference, even indirect, to medicinal products.

Article 176

General provisions on advertising of medicinal products

1. Member States shall prohibit any advertising of a medicinal product in respect of which a marketing authorisation has not been granted.

2. All parts of the advertising of a medicinal product must comply with the particulars listed in the summary of product characteristics.

3. The advertising of a medicinal product:

(a) shall encourage the rational use of the medicinal product, by presenting it objectively and without exaggerating its properties;

(b) shall be accurate, verifiable and not be misleading.

4. Any form of advertising that aims to highlight negatively another medicinal product shall be prohibited. Advertising that suggests that a medicinal product is safer or more effective than another medicinal product shall also be prohibited, unless demonstrated and supported by the summary of product characteristics.

Article 177

Restrictions on advertising of medicinal products

1. Member States shall prohibit the advertising to the general public of medicinal products that:

(a) are available on medical prescription only, in accordance with Chapter IV;

(b) contain substances classified as psychotropic or narcotic within the meaning of international conventions.

2. Medicinal products may be advertised to the general public where, by virtue of their composition and purpose, they are intended and designed for use without the intervention of a medical practitioner for diagnostic purposes or for the prescription or monitoring of treatment, with the advice of the pharmacist, if necessary.

3. Member States shall be entitled to ban, on their territory, advertising to the general public of medicinal products the cost of which may be reimbursed.

4. The prohibition contained in paragraph 1 shall not apply to vaccination campaigns carried out by the industry and approved by the competent authorities of the Member States.

5. The prohibition referred to in paragraph 1 shall apply without prejudice to Article 21 of Directive 2010/13/EU.

6. Member States shall prohibit the direct distribution of medicinal products to the public by the industry for promotional purposes.

Article 178

Advertising to the general public

1. Without prejudice to Article 177, all advertising to the general public of a medicinal product shall:

(a) be set out in such a way that it is clear that the message is an advertisement and that the product is clearly identified as a medicinal product;

(b) include the following minimum information:

(i) the name of the medicinal product, as well as the common name if the medicinal product contains only one active substance;

(ii) the information necessary for correct use of the medicinal product;

(iii) an express, legible invitation to read carefully the instructions on the package leaflet or on the outer packaging, as the case may be.

2. Member States may decide that the advertising of a medicinal product to the general public may, notwithstanding paragraph 1, include only the name of the medicinal product or its active substance, or the trademark if it is intended solely as a reminder.

Article 179

Restrictions on advertising to the general public

1. The advertising of a medicinal product to the general public shall not contain any material that:

(a) gives the impression that a medical consultation or surgical operation is unnecessary, in particular by offering a diagnosis or by suggesting treatment by mail;

(b) suggests that the effects of taking the medicinal product are guaranteed, are unaccompanied by adverse reactions or are better than, or equivalent to, those of another treatment or medicinal product;

(c) suggests that the health of the subject can be enhanced by taking the medicinal product;

(d) suggests that the health of the subject could be affected by not taking the medicinal product;

(e) is directed exclusively or principally at children;

(f) refers to a recommendation by scientists, healthcare professionals or persons who are neither of the foregoing but who, because of their celebrity, could encourage the consumption of medicinal products;

(g) suggests that the medicinal product is a food, cosmetic or other consumer product;

(h) suggests that the safety or efficacy of the medicinal product is due to the fact that it is natural;

(i) could, by a description or detailed representation of a case history, lead to erroneous self-diagnosis;

(j) refers, in improper, alarming or misleading terms, to claims of recovery;

(k) uses, in improper, alarming or misleading terms, pictorial representations of changes in the human body caused by disease or injury, or of the action of a medicinal product on the human body or parts thereof.

2. The prohibition set out in the paragraph 1, point (d), shall not apply to the vaccination campaigns referred to in Article 177(4).

Article 180

Advertising to persons qualified to prescribe, administer or supply medicinal products

1. Any advertising of a medicinal product to persons qualified to prescribe, administer or supply such products shall include:

(a) essential information compatible with the summary of product characteristics;

(b) the supply prescription status of the medicinal product.

Member States may also require such advertising to include the selling price or indicative price of the various presentations and the conditions for reimbursement by social security bodies.

2. Member States may decide that the advertising of a medicinal product to persons qualified to prescribe, administer or supply such products may, notwithstanding paragraph 1, include only the name of the medicinal product, or its international non-proprietary name, where this exists, or the trademark, if it is intended solely as a reminder.

Article 181

Supporting documentation for advertising to persons qualified to prescribe, administer or supply medicinal products

1. Any documentation relating to a medicinal product that is transmitted as part of the promotion of that medicinal product to persons qualified to prescribe, administer or supply it shall include, as a minimum, the particulars listed in Article 180(1) and shall state the date on which it was drawn up or last revised.

2. All the information contained in the documentation referred to in paragraph 1 shall be accurate, up-to-date, verifiable and sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicinal product concerned.

3. Quotations as well as tables and other illustrative matter taken from medical journals or other scientific works for use in the documentation referred to in paragraph 1 shall be faithfully reproduced and the precise sources indicated.

Article 182

Obligations related to medical sales representatives

1. Medical sales representatives shall be given adequate training by the undertaking that employs them and shall have sufficient scientific knowledge to be able to provide information that is precise and as complete as possible about the medicinal products that they promote. The information provided by medical sales representatives shall be in accordance with Article 176.

2. During each visit, medical sales representatives shall give the persons visited, or have available for them, summaries of the product characteristics of each medicinal product they present together, if the legislation of the Member State so permits, with details of the price and conditions for reimbursement referred to in Article 180(1), second subparagraph.

3. Medical sales representatives shall transmit to the scientific service referred to in Article 187(1) any information about the use of the medicinal products they advertise, with particular reference to any adverse reactions reported to them by the persons they visit.

Article 183

Promotion of medicinal products

1. Where medicinal products are being promoted to persons qualified to prescribe or supply them, no gifts, pecuniary advantages or benefits in kind may be supplied, offered or promised to such persons unless they are inexpensive and relevant to the practice of medicine or pharmacy.

2. Hospitality at sales promotion events shall always be strictly limited to their main purpose and must not be extended to persons other than persons qualified to prescribe or supply medicinal products.

3. Persons qualified to prescribe or supply medicinal products shall not solicit or accept any inducement prohibited under paragraph 1 or contrary to paragraph 2.

4. Existing measures or trade practices in Member States relating to prices, margins and discounts shall not be affected by the rules set out in paragraphs 1, 2 and 3.

Article 184

Hospitality at scientific events

The provisions of Article 183(1) shall not prevent hospitality being offered, directly or indirectly, at events for purely professional and scientific purposes. Such hospitality shall always be strictly limited to the main scientific objective of the event. It must not be extended to persons other than persons qualified to prescribe or supply medicinal products.

Article 185

Provision of samples of medicinal products

1. Free samples of medicinal products shall be provided on an exceptional basis only to persons qualified to prescribe them and on the following conditions:

   (a) the number of samples for each medicinal product each year on prescription shall be limited;

   (b) any supply of samples shall be in response to a written request, signed and dated, from the persons qualified to prescribe or supply medicinal products;

   (c) the persons qualified to supply samples shall maintain an adequate system of control and accountability;

   (d) each sample shall be no larger than the smallest presentation on the market;

   (e) each sample shall be marked 'free medical sample — not for sale' or shall show some other wording having the same meaning;

   (f) each sample shall be accompanied by a copy of the summary of product characteristics;

   (g) no samples of medicinal products containing substances classified as psychotropic or narcotic within the meaning of international conventions may be supplied.

2. On an exceptional basis, free samples of medicinal products not subject to medical prescription may also be provided to persons qualified to supply them, subject to the conditions of paragraph 1.

3. Member States may also place further restrictions on the distribution of samples of certain medicinal products.

Article 186

Implementation of advertising provisions by the Member States

1. Member States shall ensure that there are adequate and effective methods to monitor the advertising of medicinal products. Such methods, which may be based on a system of prior vetting, shall in any event include legal provisions under which persons or organisations regarded under national law as having a legitimate interest in prohibiting any advertisement inconsistent with this Chapter, may take legal action against such advertisement, or bring such advertisement before the competent authority of the Member State either to decide on complaints or to initiate appropriate legal proceedings.

2. Under the legal provisions referred to in paragraph 1, Member States shall confer upon the courts or competent authorities of the Member States powers enabling them, in cases where they deem such measures to be necessary, taking into account all the interests involved, and in particular the public interest:

(a) to order the cessation of, or to institute appropriate legal proceedings for an order for the cessation of, misleading advertising; or

(b) if misleading advertising has not yet been published but publication is imminent, to order the prohibition of, or to institute appropriate legal proceedings for an order for the prohibition of, such publication.

Member States shall confer upon the courts or competent authorities of the Member States the powers referred to in the first subparagraph, points (a) and (b), even without proof of actual loss or damage or of intention or negligence on the part of the advertiser.

3. Member States shall make provision for the measures referred to in paragraph 2 to be taken under an accelerated procedure, either with interim effect or with definitive effect.

It shall be for each Member State to decide which of the two options set out in the first subparagraph to select.

4. Member States may confer upon the courts or competent authorities of the Member States powers enabling them, with a view to eliminating the continuing effects of misleading advertising the cessation of which has been ordered by a final decision:

(a) to require publication of that decision in full or in part and in such form as they deem adequate;

(b) to require in addition the publication of a corrective statement.

5. The paragraphs 1 to 4 shall not exclude the voluntary control of advertising of medicinal products by self-regulatory bodies and recourse to such bodies, if proceedings before such bodies are possible in addition to the judicial or administrative proceedings referred to in paragraph 1.

Article 187

Implementation of advertising provisions by the marketing authorisation holder

1. The marketing authorisation holders shall establish, within their undertaking or not-for-profit entities, a scientific service in charge of information about the medicinal products that they place on the market.

2. The marketing authorisation holder shall:

(a) keep available for, or communicate to, the competent authorities of the Member States or bodies responsible for monitoring advertising of medicinal products, a sample of all advertisements emanating from its undertaking or not-for-profit entities together with a statement indicating the persons to whom it is addressed, the method of dissemination and the date of first dissemination;

(b) ensure that advertising of medicinal products by their undertaking or not-for-profit entities conforms to the requirements of this Chapter;

(c) verify that medical sales representatives employed by their undertaking or not-for-profit entities have been adequately trained and fulfil the obligations imposed upon them by Article 182, paragraphs 2 and 3;

(d) supply the competent authorities of the Member States or bodies responsible for monitoring advertising of medicinal products with the information and assistance they require to carry out their responsibilities;

(e) ensure that the decisions taken by the competent authorities of the Member States or bodies responsible for monitoring advertising of medicinal products are immediately and fully complied with.

3. The Member States shall not prohibit the co-promotion of a medicinal product by the marketing authorisation holders and one or more companies nominated by them.

Chapter XIV
Supervision and controls

SECTION 1

SUPERVISION

Article 188

System of supervision and inspections

1. The competent authority of the Member State concerned shall, in cooperation with the Agency and where relevant, other Member States, ensure compliance with the rules of this Directive, namely the principles of good manufacturing practice and good distribution practices referred to in Articles 160 and 161.

   For the purposes of the first subparagraph, the competent authority of the Member State shall have in place a system of supervision that shall include the following measures:

   (a) announced and, where appropriate, unannounced on-site inspections;

   (b) remote inspections, where justified;

   (c) compliance control measures;

   (d) the effective follow-up of the measures referred to in points (a), (b) and (c).

2. The competent authorities of the Member State concerned, and the Agency shall exchange information on the inspections referred to in paragraph 1, second subparagraph, points (a) and (b), that are planned or that have been conducted and shall cooperate in the coordination of such inspections.

3. The competent authority of the Member State shall ensure that the measures referred to in paragraph 1, second subparagraph, are carried out by the official representatives of the competent authority of the Member State:

   (a) at an appropriate frequency based on risk, at the premises or on the activities of manufacturers of medicinal products, located in the Union or in third countries, including where appropriate at central or decentralised site(s), and at the premises or on the activities of wholesale distributors of medicinal products located in the Union;

   (b) at an appropriate frequency based on risk, at the premises or on the activities of the manufacturers of active substances located in the Union or in third countries and at the premises or on the activities of importers, or distributors of active substances, located in the Union.

4. To determine the appropriate frequency based on risk referred to in paragraph 3, point (b), the competent authority of the Member State may:

(a) rely on inspection reports from trusted non-Union regulatory authorities;

(b) take into account whether the manufacturer of active substance is located in a third country included in the list referred to in Article 159(2).

5. Where the competent authority of the Member State considers it necessary, in particular where there are grounds for suspecting non-compliance with the rules of this Directive, including with the principles of good manufacturing practice and good distribution practices, referred to in Articles 160 and 161, it may have its official representatives carry out the measures referred to in paragraph 1, second subparagraph at the premises or on the activities of:

(a) manufacturers or importers of medicinal products applying for a manufacturing import authorisation or wholesale distributors applying for a wholesale distribution authorisation;

(b) manufacturers of active substance applying for a registration or manufacturing sites applying for a registration as decentralised sites;

(c) marketing authorisation holders;

(d) distributors of medicinal products or active substances located in third countries;

(e) manufacturers of excipients, functional excipients, starting materials or intermediate products located in its territory or in a third country;

(f) importers of excipients, functional excipients, starting materials or intermediate products located in its territory;

(g) persons brokering medicinal products located in its territory.

6. The measures referred to in paragraph 1, second subparagraph, may also be carried out at the request of a competent authority of a Member State, the Commission or the Agency in the Union or in third countries or, where appropriate, by asking an Official Medicines Control Laboratory or a laboratory that Member State has designated for that purpose to carry out tests on samples.

7. Each Member State shall ensure that official representatives of its competent authorities are empowered and required to carry out one or more of the following activities:

(a) inspect the manufacturing or commercial establishments of manufacturers of medicinal products, of active substances or of excipients, and any laboratories employed by the manufacturing authorisation holder to carry out verifications and controls pursuant to Article 8;

(b) take samples during an inspection or request samples as part of the measures referred to in paragraph 1, second subparagraph, including any required essential testing material or reagent with a view to independent tests being carried out by an Official Medicines Control Laboratory or a laboratory that a Member States has designated for that purpose;

(c) inspect the premises, records, documents and pharmacovigilance system master file of the marketing authorisation holder or any undertaking employed by the marketing authorisation holder to perform the activities described in Chapter IX.

8. Inspections referred to in paragraph 1, second subparagraph, points (a) and (b), shall be carried out in accordance with the principles referred to in Article 190.

9. After every inspection carried out in accordance with paragraphs 3 and 5, the competent authority of the Member State concerned shall issue a report on the compliance of the manufacturing activities inspected with the good manufacturing practice and good distribution practices referred to in Articles 160 and 161, as applicable.

10. The competent authority of the Member State that had its official representatives carry out inspections in accordance with paragraphs 3 and 5, shall share its draft report with the inspected entity.

11. Before adopting the report, the competent authority of the Member State shall give the inspected entity the opportunity to submit comments.

12. Without prejudice to any arrangements that may have been concluded between the Union and third countries, a Member State, the Commission or the Agency may require a manufacturer of a medicinal product or of an active substance established in a third country to submit to an inspection as referred to in this Article.

13. Within 90 days of the conclusion of an inspection carried out in accordace with paragraphs 3 and 5 the competent authority of the Member State concerned shall issue to the inspected entity a certificate of compliance of good manufacturing practice or good distribution practices if the outcome of that inspection shows that the inspected entity complies with the principles of good manufacturing practice or good distribution practices referred to in Articles 160 and 161.

14. If the outcome of the inspection carried out in accordance with paragraph 3, 4 and 5 shows that the inspected entity does not comply with the principles of good manufacturing practice or good distribution practices as referred to in Articles 160 and 161, the competent authority of the Member State concerned shall issue a statement of non-compliance.

15. The competent authority of the Member State shall enter the certificates of good manufacturing practice or good distribution practices in the relevant Union database managed by the Agency on behalf of the Union. Pursuant to Article 157, the competent authority of the Member States shall also enter information in that database regarding the registration of importers, manufacturers and distributors of active substances and decentralised sites performing decentralised manufacturing activities, including their respective database link to the manufacturing authorisation of the central site.

16. If the outcome of the inspection carried out in accordance with paragraph 5 is that the inspected entity does not comply with the legal requirements or the principles of good manufacturing practice or good distribution practices as referred to in Articles 160 and 161 the information shall be entered in the Union database as referred to in paragraph 15.

17. If the outcome of the activity carried out in accordance with paragraph 7, point (c), is that the marketing authorisation holder does not comply with the pharmacovigilance system as described in the pharmacovigilance system master file and with Chapter IX, the competent authority of the Member State concerned shall bring the deficiencies to the attention of the marketing authorisation holder and give the marketing authorisation holder the opportunity to submit comments.

In such case the Member State concerned shall inform the other Member States, the Agency and the Commission accordingly.

Where appropriate, the Member State concerned shall take the necessary measures to ensure that a marketing authorisation holder is subject to effective, proportionate and dissuasive penalties as laid down in Article 206.

Article 189

Cooperation on inspections

1. Upon request by one or more competent authorities, inspections referred to in Article 188, paragraphs 3 and 5, may be carried out by official representatives from more than one Member State, together with the inspectors of the Agency in accordance with Article 52(2), point (a) of [revised Regulation (EC) 726/2004] ('the joint inspection').

   The competent authority of the Member State receiving a request for a joint inspection, shall make all reasonable efforts to accept such a request, and coordinate and support that joint inspection, where:

   (a) it is demonstrated, or there are reasonable ground for suspecting, that the activities carried out on the territory of the Member State receiving the request pose a risk to the safety and quality in the Member State of the competent authority requesting the joint inspection;

   (b) competent authorities of the Member State requesting the joint inspection require specialist technical expertise available in the Member State receiving the joint inspection request;

   (c) the competent authority of the Member State receiving the request agrees that there are other reasonable grounds such as training of inspectors, sharing of good practice, for for conducting a joint inspection.

2. The competent authorities participating in a joint inspection shall conclude an agreement prior to the inspection that defines at least the following:

   (a) the scope and objective of the joint inspection;

   (b) the roles of the participating inspectors during and following the inspection, including the designation of an authority leading the inspection;

   (c) the powers and responsibilities of each of the competent authorities.

3. The competent authorities participating in the joint inspection shall commit themselves in that agreement to jointly accept the results of the inspection.

4. Where the joint inspection is conducted in one of the Member States, the competent authority leading the joint inspection shall ensure that the joint inspection is carried out in accordance with the national legislation of the Member State in which the joint inspection takes place.

5. Member States may set up joint inspection programmes to facilitate routine joint inspections. Member States may operate such programmes under a agreement as referred to in paragraphs 2 and 3.

6. A competent authority of a Member State may request another competent authority to take over one of its inspections referred to in Article 188, paragraphs 3 and 5.

7. The other competent authority of the Member State shall communicate to the requesting competent authority whether it accepts the request to conduct the inspection within 10 days. Where it accepts, it shall be responsible as the competent authority to carry out the inspections pursuant to this Section.

8. For the purposes of paragraph 6, and when the request is agreed, the requesting competent authority shall, in a timely manner, submit the relevant information necessary to conduct the inspection to the competent authority of the Member State that accepted the request.

Article 190

Inspection guidelines

1. The Commission may adopt implementing acts to lay down the principles applicable to:

   (a) the system of supervision referred to in Article 188(1);

   (b) the joint inspections referred to in Article 189(1);

   (c) the exchange of information and cooperation in the coordination of inspections in the system of supervision between the Member States and the Agency; and

   (d) trusted non-Union regulatory authorities.

   The implementing acts referred to in the first subparagraph shall be adopted in accordance with the procedure referred to in Article 214(2).

2. Member States shall, in cooperation with the Agency, establish the form and content of the manufacturing authorisation referred to in Article 142(1) and of the wholesale distribution authorisation referred to in Article 163(1), of the report referred to in Article 188, of the certificates of good manufacturing practice and of the certificates of good distribution practices referred to in Article 188(13).

SECTION 2

CONTROLS

Article 191

Controls on medicinal products

Member States shall take all appropriate measures to ensure that the marketing authorisation holder for a medicinal product and, where appropriate, the manufacturing authorisation holder, furnish proof of the controls carried out on the medicinal product or the ingredients and of the controls carried out at an intermediate stage of the manufacturing process, in accordance with the methods laid down in Annex I.

Article 192

Submission of control reports for immunological medicinal products

For the purpose of implementing Article 191, Member States may require manufacturers of immunological products to submit to a competent authority of the Member States copies of all the control reports signed by the qualified person in accordance with Article 153.

Article 193

Batch control of specific medicinal product by Member States

1. Where it considers it necessary in the interests of public health, a Member State may require the marketing authorisation holder of:

   (a) live vaccines,

   (b) immunological medicinal products used in the primary immunisation of infants or of other groups at risk,

   (c) immunological medicinal products used in public health immunisation programmes,

   (d) new immunological medicinal products or immunological medicinal products manufactured using new or altered kinds of technology or new for a particular manufacturer, during a transitional period normally specified in the marketing authorisation,

   to submit samples from each batch of the bulk or the medicinal product for examination by an Official Medicines Control Laboratory or a laboratory that a Member State has designated for that purpose before release on to the market unless the competent authority of another Member State has previously examined the batch in question and declared it to be in conformity with the approved specifications. In such a case the declaration of conformity issued by another Member States shall be directly recognised. Member States shall ensure that any such examination is completed within 30 days of the receipt of the samples.

2. Where, in the interests of public health, the laws of a Member State so provide, the competent authorities of the Member State may require the marketing authorisation holder for medicinal products derived from human blood or human plasma to submit samples from each batch of the bulk or the medicinal product for testing by an Official Medicines Control Laboratory or a laboratory that a Member State has designated for that purpose before being released into free circulation, unless the competent authorities of another Member State have previously examined the batch in question and declared it to be in conformity with the approved specifications. Member States shall ensure that any such examination is completed within 60 days of the receipt of the samples.

Article 194

Processes for the preparation of medicinal products derived from human blood or human plasma

1. Member States shall take all necessary measures to ensure that the manufacturing and purifying processes used in the preparation of medicinal products derived from human blood or human plasma are properly validated, attain batch-to-batch consistency and guarantee, insofar as the state of technology permits, the absence of specific viral contamination.

2. To this end manufacturers shall notify the competent authorities of the Member States of the method used to reduce or eliminate pathogenic viruses liable to be transmitted by medicinal products derived from human blood or human plasma. The competent authority of the Member State may submit samples of the bulk or the medicinal product for testing by a State laboratory or a laboratory designated for that

purpose, either during the examination of the application pursuant to Article 29, or after a marketing authorisation has been granted.

Chapter XV
Restrictions of marketing authorisations

Article 195

Suspending, revoking or varying the terms of marketing authorisations

1. The competent authorities of the Member States or, in the case of centralised marketing authorisation, the Commission shall suspend, revoke or vary a marketing authorisation if the view is taken that the medicinal product is harmful or that it lacks therapeutic efficacy, or that the benefit-risk balance is not favourable, or that its qualitative and quantitative composition is not as declared. Therapeutic efficacy shall be considered to be lacking when it is concluded that therapeutic results cannot be obtained from the medicinal product.

2. The competent authorities of the Member States or, in the case of centralised marketing authorisation, the Commission may suspend, revoke or vary a marketing authorisation if a serious risk to the environment or public health has been identified and not sufficiently addressed by the marketing authorisation holder.

3. A marketing authorisation may also be suspended, revoked or varied where the particulars supporting the application as provided for in Articles 6, 9 to 14 or Annexes I to V are incorrect or have not been amended in accordance with Article 90, or where any conditions referred to in Articles 44, 45 and 87 have not been fulfilled or where the controls referred to in Article 191 have not been carried out.

4. Paragraph 2 also applies in cases where the manufacture of the medicinal product is not carried out in compliance with the particulars provided pursuant to Annex I, or where controls are not carried out in compliance with the control methods described pursuant to Annex I.

5. The competent authorities of the Member State or, in the case of centralised marketing authorisation, the Commission shall suspend or revoke the marketing authorisation for a category of preparations or all preparations where any one of the requirements laid down in Article 143 is no longer met.

Article 196

Prohibition of supply or withdrawal of a medicinal product from the market

1. Without prejudice to the measures provided for in Article 195, the competent authorities of the Member States and, in the case of centralised marketing authorisation, the Commission shall take all appropriate steps to ensure that the supply of the medicinal product is prohibited and the medicinal product withdrawn from the market, if the view is taken that:

   (a) the medicinal product is harmful;

   (b) it lacks therapeutic efficacy;

   (c) the benefit-risk balance is not favourable;

   (d) its qualitative and quantitative composition is not as declared;

(e) the controls on the medicinal product or on the ingredients and the controls at an intermediate stage of the manufacturing process have not been carried out or if some other requirement or obligation relating to the grant of the manufacturing authorisation has not been fulfilled; or

(f) a serious risk to the environment or to public health via the environment has been identified and not sufficiently addressed by the marketing authorisation holder.

2. The competent authority of the Member State or, in the case of centralised marketing authorisation, the Commission may limit the prohibition to supply the product, or its withdrawal from the market, to those batches that are the subject of dispute.

3. The competent authority of the Member State or, in the case of centralised marketing authorisation, the Commission may, for a medicinal product for which the supply has been prohibited or that has been withdrawn from the market in accordance with paragraphs 1 and 2, in exceptional circumstances during a transitional period allow the supply of the medicinal product to patients who are already being treated with the medicinal product.

Article 197

Suspected falsified medicinal products and medicinal products with suspected quality defects

1. Member States shall have a system in place that aims at preventing medicinal products that are suspected to present a danger to health from reaching the patient.

2. The system referred to in paragraph 1 shall cover the receipt and handling of notifications of suspected falsified medicinal products as well as of medicinal products with suspected quality defects. The system shall also cover recalls of medicinal products by marketing authorisation holders or withdrawals of medicinal products from the market ordered by competent authorities of the Member States or, in the case of centralised marketing authorisation, the Commission from all relevant actors in the supply chain both during and outside normal working hours. The system shall also make it possible to recall, where necessary with the assistance of health professionals, medicinal products from patients who received such products.

3. If the medicinal product in question is suspected of presenting a serious risk to public health, the competent authority of the Member State in which that product was first identified shall, without undue delay, transmit a rapid alert notification to all Member States and all actors in the supply chain in that Member State. In the event of such medicinal products being deemed to have reached patients, urgent public announcements shall be issued within 24 hours in order to recall those medicinal products from the patients. Those announcements shall contain sufficient information on the suspected quality defect or falsification and the risks involved.

Article 198

Suspending or revoking manufacturing authorisation

In addition to the measures specified in Article 196, the competent authority of the Member State may suspend manufacture or imports of medicinal products coming from third countries, or suspend or revoke the manufacturing authorisation for a category of preparations or all preparations where Articles 144, 147, 153 and 191 are not complied with.

Article 199

Refusal, suspension or revocation within the limits of the Directive

1. An authorisation to market a medicinal product shall not be refused, suspended or revoked except on the grounds set out in this Directive.

2. No decision concerning suspension of manufacture or of importation of medicinal products coming from third countries, prohibition of supply or withdrawal from the market of a medicinal product may be taken except on the grounds set out in Articles 195(5) and 196.

Chapter XVI
General provisions

Article 200

Competent authorities of the Member States

1. Member States shall designate the competent authorities to carry out tasks under this Directive.

2. Member States shall ensure that adequate financial resources are available to provide the staff and other resources necessary for the competent authorities to carry out the activities required by this Directive and [revised Regulation (EC) No 726/2004].

3. The competent authorities of the Member States shall cooperate with each other and with the Agency and the Commission in the performance of their tasks under this Directive and [revised Regulation (EC) No 726/2004] to ensure proper application and due enforcement. The competent authorities of the Member States shall transmit to each other all necessary information.

4. The competent authority of the Member State may process personal health data from sources other than clinical studies to support their public health tasks and, in particular, the evaluation and monitoring to medicinal products, for the purpose of improving the robustness of the scientific assessment or verifying claims of the applicant or marketing authorisation holder.

   Processing of personal data under this Directive shall be subject to Regulations (EU) 2016/679 and (EU) 2018/1725, as applicable.

Article 201

Cooperation with other authorities

1. Member States, in applying this Directive, shall ensure that when questions arise with regard to the regulatory status of a medicinal product, in relation to their link to substances of human origin as referred to in Regulation (EU) No [SoHO Regulation], the competent authorities of the Member States shall consult the relevant authorities established under that Regulation.

2. Member States, in applying this Directive, shall take the necessary measures to ensure cooperation between competent authorities for medicinal products and customs authorities.

Article 202

Member States exchange of information of manufacturing or wholesale distribution authorisations of medicinal products

1. Member States shall take all appropriate measures to ensure that the competent authorities of the Member States concerned communicate to each other such information as is appropriate to guarantee that the requirements placed on the authorisations referred to in Articles 142 and 163, on the certificates referred to in Article 188(13) or on the marketing authorisations are fulfilled.

2. Upon reasoned request, Member States shall send electronically the report referred to in with Article 188 to the competent authorities of another Member State or to the Agency.

3. The conclusions reached in accordance with Articles 188(13) or 188(14) shall be valid throughout the Union.

4. However, in exceptional cases, if a Member State is unable, for reasons relating to public health, to accept the conclusions reached following an inspection under Article 188(1), that Member State shall without undue delay inform the Commission and the Agency. The Agency shall inform the Member States concerned.

5. When the Commission is informed of these divergences of opinion, it may, after consulting the Member States concerned, ask the inspector who performed the original inspection to perform a new inspection; the inspector may be accompanied by two other inspectors from Member States that are not parties to the disagreement.

Article 203

Information on prohibition of supply or other action on a marketing authorisation

1. Each Member State shall take all the appropriate measures to ensure that decisions granting marketing authorisation, refusing or revoking a marketing authorisation, cancelling a decision refusing or revoking a marketing authorisation, prohibiting supply, or withdrawing a product from the market, together with the reasons on which such decisions are based, are brought to the attention of the Agency without undue delay.

2. In addition to the notification made pursuant to Article 116 of [revised Regulation (EC) No 726/2004], the marketing authorisation holder shall declare without undue delay if such notified action is based on any of the grounds set out in Articles 195 or 196(1).

3. The marketing authorisation holder shall also make the notification pursuant to paragraph 2 in cases where the action is taken in a third country and where such action is based on any of the grounds set out Articles 195 or 196(1).

4. The marketing authorisation holder shall furthermore notify the Agency where the action referred to in paragraphs 2 or 3 is based on any of the grounds referred to in Articles 195 or 196(1).

5. The Agency shall forward notifications received in accordance with paragraph 4 to all Member States without undue delay.

6. Member States shall ensure that appropriate information about action taken pursuant to paragraphs 1 and 2 that may affect the protection of public health in third countries

is without undue delay brought to the attention of the World Health Organization, with a copy to the Agency.

7. Each year, the Agency shall make public a list of the medicinal products for which marketing authorisations have been refused, revoked or suspended in the Union, whose supply has been prohibited or that have been withdrawn from the market, including the reasons for such action.

Article 204

Notification of decisions related to marketing authorisations

1. Every decision referred to in this Directive that is taken by the competent authority of a Member State shall state in detail the reasons on which it is based.

2. Such decision shall be notified to the party concerned, together with information as to the redress available to them under the laws in force and of the time limit allowed for access to such redress.

3. Decisions to grant or revoke a marketing authorisation shall be made publicly available.

Article 205

Authorisation of a medicinal product on public health grounds

1. In the absence of a marketing authorisation or of a pending application for a medicinal product authorised in another Member State in accordance with Chapter III, a Member State may for justified public health reasons authorise the placing on the market of the said medicinal product.

2. When a Member State avails itself of this possibility, it shall adopt the necessary measures in order to ensure that the requirements of this Directive are complied with, in particular those referred to in Chapters IV, VI, IX, XIII and XIV, and Article 206. Member States may decide that Article 74, paragraphs 1 to 3, shall not apply to medicinal products authorised under paragraph 1.

3. Before granting such a marketing authorisation, a Member State:

   (a) shall notify the marketing authorisation holder, in the Member State in which the medicinal product concerned is authorised, of the proposal to grant a marketing authorisation under this Article in respect of the medicinal product concerned;

   (b) may request the competent authority in that Member State to submit copies of the assessment report referred to in Article 43(5) and of the marketing authorisation in force in respect of the medicinal product concerned. If so requested, the competent authority in that Member State shall supply, within 30 days of receipt of the request, a copy of the assessment report and the marketing authorisation in respect of the medicinal product concerned.

4. The Commission shall set up a publicly available register of medicinal products authorised under paragraph 1. Member States shall notify the Commission if any medicinal product is authorised, or ceases to be authorised, under paragraph 1, including the name or corporate name and permanent address of the marketing authorisation holder. The Commission shall amend the register of medicinal products accordingly and make this register available on their website.

Article 206

Penalties

1. Member States shall lay down the rules on penalties applicable to infringements of national provisions adopted pursuant to this Directive and shall take all measures necessary to ensure that they are implemented. The penalties must be effective, proportionate and dissuasive. Member States shall, without delay, notify the Commission of those rules and of those measures and shall notify without delay of any subsequent amendment affecting them.

   Those penalties shall not be inferior to those applicable to infringements of national law of similar nature and importance.

2. The rules referred to in paragraph 1, first subparagraph, shall address, inter alia, the following:

   (a) the manufacturing, distribution, brokering, import and export of falsified medicinal products, as well as sale at distance of falsified medicinal products to the public;

   (b) non-compliance with the provisions laid down in this Directive on manufacturing, distribution, import and export of active substances;

   (c) non-compliance with the provisions laid down in this Directive on the use of excipients;

   (d) non-compliance with the provisions laid down in this Directive on pharmacovigilance;

   (e) non-compliance with the provisions laid down in this Directive on advertising.

3. Where relevant, the penalties shall take into account the risk to public health presented by the falsification of medicinal products.

Article 207

Collection of unused or expired medicinal products

Member States shall ensure that appropriate collection systems are in place for medicinal products that are unused or have expired.

Article 208

Declaration of interests

1. In order to guarantee independence and transparency, the Member States shall ensure that members of staff of the competent authority responsible for granting authorisations, rapporteurs and experts concerned with the authorisation and surveillance of medicinal products have no financial or other interests in the pharmaceutical industry that could affect their impartiality. These persons shall make an annual declaration of their financial interests.

2. In addition, the Member States shall ensure that the competent authority makes publicly available its rules of procedure and those of its committees, agendas for its meetings and records of its meetings, accompanied by decisions taken, details of votes and explanations of votes, including minority opinions.

Chapter XVII
Specific provisions concerning Cyprus, Ireland, Malta and the United Kingdom in respect of Northern Ireland

Article 209

Provisions relevant to the United Kingdom in respect of Northern Ireland

1. By way of derogation from Article 5, the competent authorities of the United Kingdom in respect of Northern Ireland may temporarily authorise the supply to patients in Northern Ireland of a medicinal product belonging to the categories referred to in Article 3, paragraphs 1 and 2 of [revised Regulation (EC) No 726/2004] provided that all of the following conditions are fulfilled:

   (a) the medicinal product concerned has been granted a marketing authorisation by the competent authority of the United Kingdom for parts of the United Kingdom other than Northern Ireland;

   (b) the medicinal product concerned is only made available to patients or end-consumers in the territory of Northern Ireland and is not made available in any Member State.

   The maximum validity of the temporary authorisation shall be six months.

   Notwithstanding the specified validity, the temporary authorisation shall cease to be valid if the medicinal product concerned has been granted a marketing authorisation in accordance with Article 13 of [revised Regulation (EC) No 726/2004], or if such marketing authorisation has been refused in accordance with that Article.

2. By way of derogation from Article 56(4), marketing authorisations may be granted by the competent authorities of the United Kingdom in respect of Northern Ireland:

   (a) to applicants established in parts of the United Kingdom other than Northern Ireland;

   (b) to marketing authorisation holders established in parts of the United Kingdom other than Northern Ireland, in accordance with the mutual recognition or the decentralised procedure laid down in Chapter III, Sections 3 and 4.

   The competent authorities of the United Kingdom in respect of Northern Ireland may extend marketing authorisations already granted prior to 20 April 2022 to marketing authorisation holders established in parts of the United Kingdom other than Northern Ireland.

3. By way of derogation from Article 33, paragraphs 1, 3 and 4 and Article 35(1), if an application for marketing authorisation is submitted in one or more Member States and in the United Kingdom in respect of Northern Ireland, or if an application for marketing authorisation is submitted in the United Kingdom in respect of Northern Ireland for a medicinal product that is already being examined or has already been authorised in a Member State, the application regarding the United Kingdom in respect of Northern Ireland shall not have to be submitted in accordance with Chapter III, Sections 3 and 4, provided that all of the following conditions are fulfilled:

   (a) the marketing authorisation for the United Kingdom in respect of Northern Ireland is granted by the competent authority for the United Kingdom in

respect of Northern Ireland in compliance with Union law, and such compliance with Union law is ensured during the period of validity of that marketing authorisation;

(b) the medicinal products authorised by the competent authority for the United Kingdom in respect of Northern Ireland are made available to patients or end-consumers only in the territory of Northern Ireland, and they are not made available in any Member State.

4. The marketing authorisation holder of a medicinal product for which a marketing authorisation has already been granted for the United Kingdom in respect of Northern Ireland in accordance with Chapter III, Sections 3 and 4, before 20 April 2022 shall be allowed to withdraw the marketing authorisation for the United Kingdom in respect of Northern Ireland from the mutual recognition or the decentralised procedure and to submit an application for a marketing authorisation for that medicinal product to the competent authorities of the United Kingdom with respect to Northern Ireland in accordance with paragraph 1.

5. With regard to quality control testing referred to in Article 8 carried out in parts of the United Kingdom other than Northern Ireland regarding medicinal products included in the list referred to in Article 211(9) other than those authorised by the Commission, the competent authorities of the United Kingdom in respect of Northern Ireland may consider that there is a justifiable case within the meaning of Article 8, point (b), without carrying out a case-by-case assessment provided that:

(a) each batch of the medicinal products concerned is released by a qualified person on a site in the Union or in Northern Ireland or by a qualified person on a site in parts of the United Kingdom other than Northern Ireland applying quality standards that are equivalent to those laid down in Article 153;

(b) the establishment designated by the third party conducting the quality control testing is supervised by the competent authority of the United Kingdom, including by performing on-the-spot checks;

(c) where the batch release is carried out by a qualified person who resides and operates in parts of the United Kingdom other than Northern Ireland, the manufacturing authorisation holder declares that it does not have at its disposal a qualified person who resides and operates in the Union on 20 April 2022.

6. By way of derogation from Article 142(1), the competent authorities of the United Kingdom in respect of Northern Ireland shall allow medicinal products to be imported from parts of the United Kingdom other than Northern Ireland by a wholesale distribution authorisation holders as referred to in Article 163(1) that are not in possession of a relevant manufacturing authorisation provided that all of the following conditions are fulfilled:

(a) the medicinal products have undergone quality control testing either in the Union, as provided for in Article 153(3), or in parts of the United Kingdom other than Northern Ireland in compliance with Article 8, point (b);

(b) the medicinal products have been subject to batch release by a qualified person in the Union in accordance with Article 153(1) or, for medicinal products authorised by the United Kingdom in respect of Northern Ireland, in parts of the United Kingdom other than Northern Ireland applying quality standards that are equivalent to those laid down in Article 153(1);

(c) the marketing authorisation for the medicinal product concerned has been granted in accordance with Union law, by the competent authority of a Member State or by the Commission or, as regards medicinal products placed on the market in Northern Ireland, by the competent authority of the United Kingdom in respect of Northern Ireland;

(d) medicinal products are only made available to patients or end-consumers in the Member State into which the medicinal products are imported, or, if imported into Northern Ireland, are only made available to patients or end-consumers in Northern Ireland;

(e) the medicinal products bear the safety features referred to in Article 67.

7. For batches of medicinal products that are exported to parts of the United Kingdom other than Northern Ireland from a Member State and subsequently imported into Northern Ireland, the controls upon importation referred to in Article 153(1), first and second subparagraphs, shall not be required, provided that those batches have undergone such controls in a Member State prior to being exported to parts of the United Kingdom other than Northern Ireland and that they are accompanied by the control reports referred to in Article 153(1), third subparagraph.

8. Where the manufacturing authorisation is granted by the competent authority of the United Kingdom in respect of Northern Ireland, the qualified person referred to in Article 151(1) may reside and operate in parts of the United Kingdom other than Northern Ireland. This paragraph shall not apply where the manufacturing authorisation holder already has at its disposal a qualified person who resides and operates in the Union on 20 April 2022.

9. By way of derogation from the Article 99(5), where the marketing authorisation is granted by the competent authority of United Kingdom in respect of Northern Ireland, the qualified person referred to in Article 99(4), point (a), may reside and operate in parts of the United Kingdom other than Northern Ireland. This paragraph shall not apply where the marketing authorisation holder already has at its disposal a qualified person who resides and operates in the Union on 20 April 2022.

10. The competent authorities of the United Kingdom in respect of Northern Ireland shall publish on their website a list of medicinal products to which they have applied or intend to apply the derogations as set out in this Article and shall ensure that the list is updated and managed in an independent manner, at least on a six-monthly basis.

Article 210

Regulatory functions carried out in the United Kingdom

1. The Commission shall continuously monitor developments in the United Kingdom that could affect the level of protection regarding the regulatory functions referred to in Article 99(4), Article 151(3), Article 211, paragraphs 1, 2, 5 and 6, Article 209, paragraphs 6 and 7, that are carried out in parts of the United Kingdom other than Northern Ireland taking into account, in particular, the following elements:

(a) the rules governing the granting of marketing authorisations, the obligations of the marketing authorisation holder, the granting of manufacturing authorisations, the obligations of the manufacturing authorisation holder, the

qualified persons and their obligations, quality control testing, batch release and pharmacovigilance as laid down in United Kingdom law;

(b) whether the competent authorities of the United Kingdom ensure the effective enforcement within their territory of the rules referred to in point (a), by means of, inter alia, inspections and audits of marketing authorisation holders, manufacturing authorisation holders and wholesale distributors located in their territories, and on-the-spot checks at their premises regarding the exercise of the regulatory functions referred to in point (a).

2. Where the Commission finds that the level of protection of public health ensured by the United Kingdom through rules governing the production, distribution and use of medicinal products as well as the effective enforcement of those rules is no longer essentially equivalent to that guaranteed within the Union, or where sufficient information is not available to the Commission to enable it to establish whether an essentially equivalent level of protection of public health is ensured by the United Kingdom, the Commission shall inform the United Kingdom through a written notification of that finding and of the detailed reasons therefor.

For a period of six months following the written notification made pursuant to the first subparagraph, the Commission shall enter into consultations with the United Kingdom with a view to remedying the situation giving rise to that written notification. In justified cases, the Commission may extend that period by three months.

3. If the situation giving rise to the written notification made pursuant to paragraph 2, first subparagraph, is not remedied within the time limit referred to in paragraph 2, second subparagraph, the Commission shall be empowered to adopt a delegated act amending or supplementing the provisions among those referred to in paragraph 1 whose application shall be suspended.

4. Where a delegated act pursuant to paragraph 3 has been adopted, the provisions referred to in the introductory sentence of paragraph 1 as specified in the delegated act shall cease to apply on the first day of the month following the entry into force of the delegated act.

5. Where the situation giving rise to the adoption of the delegated act pursuant to paragraph 3 has been remedied, the Commission shall adopt a delegated act specifying those suspended provisions that shall apply again. In that case, the provisions specified in the delegated act adopted pursuant to this paragraph shall apply again on the first day of the month following the entry into force of the delegated act referred to in this paragraph.

Article 211

Provisions relevant to Cyprus, Ireland and Malta and applicable until 31 December 2024

1. By way of derogation from Article 56(4), marketing authorisations may be granted in accordance with the mutual recognition or the decentralised procedure laid down in Chapter III, Sections 3 and 4, to marketing authorisation holders established in parts of the United Kingdom other than Northern Ireland.

Until 31 December 2024, the competent authorities of Cyprus, Ireland and Malta marketing authorisations already granted prior to 20 April 2022 may be extended to

marketing authorisation holders established in parts of the United Kingdom other than Northern Ireland.

The marketing authorisations granted or extended by the competent authorities of Cyprus, Ireland or Malta in accordance with the first and second subparagraphs shall cease to be valid at the latest on 31 December 2026.

2. With regard to quality control testing referred to in Article 8 carried out in parts of the United Kingdom other than Northern Ireland regarding medicinal products included in the list referred to in paragraph 9, other than those authorised by the Commission, and, until 31 December 2024, the competent authorities of Cyprus, Ireland and Malta may consider that there is a justifiable case within the meaning of Article 8, point (b), without carrying out a case-by-case assessment provided that:

(a) each batch of the medicinal products concerned is released by a qualified person on a site in the Union or in Northern Ireland or by a qualified person on a site in parts of the United Kingdom other than Northern Ireland applying quality standards that are equivalent to those laid down in Article 153(1);

(b) the establishment designated by the third party conducting the quality control testing is supervised by the competent authority of the United Kingdom, including by performing on-the-spot checks;

(c) where the batch release is carried out by a qualified person who resides and operates in parts of the United Kingdom other than Northern Ireland, the manufacturing authorisation holder declares that it does not have at its disposal a qualified person who resides and operates in the Union on 20 April 2022.

3. By way of derogation from Article 142(1), the competent authorities of Cyprus, Ireland and Malta shall allow medicinal products to be imported from parts of the United Kingdom other than Northern Ireland by wholesale distribution authorisation holders as referred to in Article 163(1) that are not in possession of a relevant manufacturing authorisation provided that all of the following conditions are fulfilled:

(a) the medicinal products have undergone quality control testing either in the Union, as provided for in Article 153(3), or in parts of the United Kingdom other than Northern Ireland in compliance with Article 8, point (b);

(b) the medicinal products have been subject to batch release by a qualified person in the Union in accordance with Article 153(1) or, for medicinal products authorised by the competent authorities the United Kingdom in respect of Northern Ireland, in parts of the United Kingdom other than Northern Ireland applying quality standards that are equivalent to those laid down in Article 153(1);

(c) the marketing authorisation for the medicinal product concerned has been granted in accordance with Union law, by the competent authority of a Member State or by the Commission or, as regards medicinal products placed on the market in Northern Ireland, by the competent authority of the United Kingdom in respect of Northern Ireland;

(d) medicinal products are only made available to patients or end-consumers in the Member State into which the medicinal products are imported, or, if imported into Northern Ireland, are only made available to patients or end-consumers in Northern Ireland;

(e) the medicinal products bear the safety features referred to in Article 67.

Article 166(1), point (b), shall not apply to imports that fulfil the conditions laid down in the first subparagraph.

4. For batches of medicinal products that are exported to parts of the United Kingdom other than Northern Ireland from a Member State and subsequently imported until 31 December 2024 into Cyprus, Ireland or Malta, the controls upon importation referred to Article 153(1), first and second subparagraphs, shall not be required, provided that those batches have undergone such controls in a Member State prior to being exported to parts of the United Kingdom other than Northern Ireland and that they are accompanied by the control reports referred to in Article 153(1), third subparagraph.

5. By way of derogation from Article 205(1) until 31 December 2024, in the absence of a marketing authorisation or of a pending application for a marketing authorisation the competent authorities of Cyprus and Malta may authorise for justified public health reasons the placing on their national market of a medicinal product authorised in parts of the United Kingdom other than Northern Ireland.

The competent authorities of Cyprus and Malta may also maintain in force or, until 31 December 2024, extend marketing authorisations that were granted pursuant to Article 205(1) before 20 April 2022 and that authorise the placing on their national market of a medicinal product authorised in parts of the United Kingdom other than Northern Ireland.

Authorisations that are granted, extended or maintained in force pursuant to the first or second subparagraphs shall not be valid after 31 December 2026.

6. By way of derogation from Article 56(4), the competent authorities of Malta and Cyprus may grant marketing authorisations as referred to in paragraph 5 to marketing authorisation holders established in parts of the United Kingdom other than Northern Ireland.

7. Where the competent authorities of Cyprus or Malta grant or extend a marketing authorisation as referred to in paragraph 5, they shall ensure compliance with the requirements of this Directive.

8. Before granting a marketing authorisation pursuant to paragraph 5, the competent authorities of Cyprus or Malta:

(a) shall notify the marketing authorisation holder in parts of the United Kingdom other than Northern Ireland of the proposal to grant a marketing authorisation or to extend a marketing authorisation under paragraphs 5 to 8 in respect of the medicinal product concerned;

(b) may request the competent authority in the United Kingdom to submit the relevant information regarding the marketing authorisation of the medicinal product concerned.

9. The competent authorities of Cyprus, Ireland, Malta shall publish on their website a list of medicinal products to which they have applied or intend to apply the derogations as set out in this Article and shall ensure that the list is updated and managed in an independent manner, at least on a six-monthly basis.

Article 212

Derogations for medicinal products placed on the markets of Cyprus, Ireland, Malta or Northern Ireland

The derogations set out in Article 211, paragraphs 1 and 6, Article 8, Article 209, paragraphs 6 and 7, Article 153 (3), Article 99(4) and Article 211(5) shall not affect the obligations of the marketing authorisation holder to ensure the quality, safety and efficacy of the medicinal product placed on the markets of Cyprus, Ireland, Malta or Northern Ireland laid down in this Directive.

Chapter XVIII
Final provisions

Article 213

Amendment to the Annexes

The Commission is empowered to adopt delegated acts in accordance with Article 215 amending Annexes I to VI in order to adapt them to scientific and technical progress and amend Article 22 with regard to the ERA requirements set out in paragraphs 2, 3, 4 and 6 of that Article.

Article 214

Standing Committee on Medicinal Products for Human Use

1. The Commission shall be assisted by the Standing Committee on Medicinal Products for Human Use. That Committee shall be a committee within the meaning of Regulation (EU) No 182/2011.
2. Where reference is made to this paragraph, Article 5 of Regulation (EU) No 182/2011 shall apply.
3. Where the opinion of the Committee is to be obtained by written procedure and reference is made to this paragraph, that procedure shall be terminated without result only when, within the time limit for delivery of the opinion, the chair of the Committee so decides.
4. The rules of procedure of the Standing Committee on Medicinal Products shall be made publicly available.
5. The Standing Committee on Medicinal Products for Human Use shall ensure that its rules of procedure are adapted to the need to make medicinal products swiftly available to patients and take account of the tasks incumbent upon it under Chapter III and the procedure set out in Article 42.

Article 215

Exercise of the delegations

1. The power to adopt delegated acts is conferred on the Commission subject to the conditions laid down in this Article.
2. The power to adopt delegated acts referred to in Articles 4(2), 24(5), 25(9), 26(3), 28, paragraphs 2 and 3, 27(3), 63(5), 65(2), 67(2), 88(1), 92(4), 126(1), 150(3), 153(4), 161, 210(4) and 213 shall be conferred on the Commission for a period of five years

from [OP please insert the date of the entry into force of this Directive]. The Commission shall draw up a report in respect of the delegation of power not later than nine months before the end of the five-year period. The delegation of power shall be tacitly extended for periods of an identical duration, unless the European Parliament or the Council opposes such extension not later than three months before the end of each period.

The power to adopt delegated acts referred to in Article 210, paragraphs 3 and 5, shall be conferred on the Commission for an indeterminate period of time from [OP please insert the date = the date of the entry into force of this Directive].

3. The delegation of power referred to in Articles 4(2), 24(5), 25(9), 26(3), 27(3), 28, paragraphs 2 and 3, 63(5), 65(2), 67(2), 88(1), 92(4), 126(1), 150(3), 153(4), 161, 210(4) and 213 may be revoked at any time by the European Parliament or by the Council. A decision to revoke shall put an end to the delegation of the power specified in that decision. It shall take effect the day following the publication of the decision in the *Official Journal of the European Union* or at a later date specified therein. It shall not affect the validity of any delegated acts already in force.

4. Before adopting a delegated act, the Commission shall consult experts designated by each Member State in accordance with the principles laid down in the Interinstitutional Agreement of 13 April 2016 on Better Law-Making.

5. As soon as it adopts a delegated act, the Commission shall notify it simultaneously to the European Parliament and to the Council.

6. A delegated act adopted pursuant to Articles 6(2), 26(3), 24(5), 28, paragraphs 2 and 3, 27(3), 63(5), 65(2), 67(2), 88(1), 92(4), 126(1), 150(3), 153(4), 161, 210(4) and 213 shall enter into force only if no objection has been expressed either by the European Parliament or by the Council within a period of two months of notification of that act to the European Parliament and the Council or if, before the expiry of that period, the European Parliament and the Council have both informed the Commission that they will not object. That period shall be extended by two months at the initiative of the European Parliament or of the Council.

Article 216

Report

By [OP please insert the date = 10 years following 18 months after the date of entering into force of this Directive], the Commission shall present a report to the European Parliament and the Council on the application of this Directive, including an assessment of the fulfilment of its objectives and the resources required to implement it.

Article 217

Repeals

1. Directive 2001/83/EC is repealed with effect from [OP please insert the date = 18 months after the date of entering into force of this Directive].

2. Directive 2009/35/EC is repealed with effect from [OP please insert the date = 18 months after the date of entering into force of this Directive].

3. References to the repealed Directives 2001/83/EC and 2009/35/EC shall be construed as references to this Directive. References to the repealed Directive 2001/83/EC shall be read in accordance with the correlation table in Annex VIII.

Article 218

Transitional provisions

1. The procedures concerning the applications for marketing authorisations for medicinal products validated in accordance with Article 19 of Directive 2001/83/EC before [OP please insert the date = 18 months after the date of entering into force of this Directive] and that were pending on [OP please insert the date = the day before 18 months after the date of entering into force of this Directive] shall be completed in accordance with Article 29.

2. Procedures initiated on the basis of Articles 29, 30, 31, and 107i of Directive 2001/83/EC before [OP please insert the date = 18 months after the date of entering into force of this Directive] and that were pending on [OP please insert the date = the day before 18 months after the date of entering into force of this Directive] shall be completed in accordance with Articles 32 to 34 or Article 107k, as appropriate, of that Directive as applicable on [OP please insert the date = the day before 18 months after the date of entering into force of this Directive].

3. This Directive shall also apply to medicinal products authorised in accordance with Directive 2001/83/EC before [OP please insert the date = 18 months after the date of entering into force of this Directive].

   This Directive shall also apply to registrations of homeopathic medicinal products and traditional herbal medicinal products carried out in accordance with Directive 2001/83/EC before [OP please insert the date = 18 months after the date of entering into force of this Directive].

4. By way of derogation from Chapter VI, the medicinal products placed on the market in accordance with Directive 2001/83/EC before [OP please insert the date = 18 months after the date of entering into force of this Directive] may continue to be made available on the market until [OP please insert the date = five years after 18 months after the date of entering into force of this Directive], provided that they comply with the provision on labelling and package leaflet set out in Title V of Directive 2001/83/EC as applicable on [OP please insert the date = the day before 18 months after the date of entering into force of this Directive].

5. By way of derogation from Article 81, reference medicinal products for which the application for marketing authorisation has been submitted before [OP please insert the date = 18 months after the date of entering into force of this Directive] shall be subject to the provisions on data protection periods set out in Article 10 of Directive 2001/83/EC as applicable on [OP please insert the date = 18 months after the date of entering into force of this Directive] until [OP please insert the date = 18 months after the date of entering into force of this Directive].

6. By way of derogation from paragraph 3, the reporting obligations as referred to in Article 57, shall not apply with regards to medicinal products authorised in accordance with Directive 2001/83/EC before [OP please insert the date = 18 months after the date of entering into force of this Directive].

Article 219

Transposition

1. Member States shall bring into force the laws, regulations and administrative provisions to comply with this Directive by [18 months after the date of entering into force of this Directive]. They shall immediately communicate the text of those measures to the Commission.

2. When Member States adopt those measures, they shall contain a reference to this Directive or be accompanied by such reference on the occasion of their official publication. They shall also include a statement that references in existing laws, regulations and administrative provisions to the Directives repealed by this Directive shall be construed as references to this Directive. Member States shall determine how such reference is to be made and how that statement is to be formulated.

3. Member States shall communicate to the Commission the text of the main measures of national law that they adopt in the field covered by this Directive.

Article 220

Entry into force

This Directive shall enter into force on the twentieth day following that of its publication in the *Official Journal of the European Union*.

Article 221

Addressees

This Directive is addressed to the Member States.

Done at Brussels,

For the European Parliament	*For the Council*
The President	*The President*

EUROPEAN
COMMISSION

Brussels, 26.4.2023
COM(2023) 193 final

2023/0131 (COD)

Proposal for a

REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, amending Regulation (EC) No 1394/2007 and Regulation (EU) No 536/2014 and repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006

(Text with EEA relevance)

{SEC(2023) 390 final} - {SWD(2023) 192 final} - {SWD(2023) 193 final} - {SWD(2023) 194 final}

EXPLANATORY MEMORANDUM

1. CONTEXT OF THE PROPOSAL

• Reasons for and objectives of the proposal

EU pharmaceutical legislation has enabled the authorisation of safe, efficacious and high-quality medicinal products. However, patient access to medicinal products across the EU and security of supply are growing concerns, mirrored by recent Council conclusions[1] and resolutions of the European Parliament[2]. There is also a growing problem of shortages of medicinal products for many EU/EEA countries. Consequences of such shortages include decreased quality of treatment received by patients and increased burden on health systems and on healthcare professionals, who need to identify and provide alternative treatments. While the pharmaceutical legislation creates regulatory incentives for innovation and regulatory tools to support timely authorisation of innovative and promising therapies, these products do not always reach the patient, and patients in the EU have differing levels of access.

Moreover, innovation is not always focused on unmet medical needs, and there are market failures, especially in the development of priority antimicrobials that can help address antimicrobial resistance. Scientific and technological developments and digitalisation are not fully exploited, while the environmental impact of medicinal products needs attention. In addition, the authorisation system could be simplified to keep up with global regulatory competition. The pharmaceutical strategy for Europe[3] is a holistic answer to the current challenges of the pharmaceutical policy with legislative and non-legislative actions interacting together to achieve its overall goal of ensuring EU's supply of safe and affordable medicinal products and supporting the EU pharmaceutical industry's innovation efforts[4]. Reviewing the pharmaceutical legislation is key to achieving these objectives. However, innovation, access and affordability are also influenced by factors outside the scope of this legislation, such as global research and innovation activities or national pricing and reimbursement decisions. Hence, not all problems can be addressed by the revision of the legislation alone. Despite this, EU pharmaceutical legislation can be an enabling and connecting factor for innovation, access, affordability and environmental protection.

The proposed revision of the EU pharmaceutical legislation builds on the high level of public health protection and harmonisation already achieved for the authorisation of medicinal products. The overarching aim of the reform is to ensure that patients across the EU have timely and equitable access to medicines. Another objective of the proposal is to enhance security of supply and address shortages through specific measures, including stronger obligations on marketing authorisation holders to notify potential or actual shortages and marketing withdrawals, cessations and suspensions

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1 Council conclusions on strengthening the balance in the pharmaceutical systems in the EU and its Member States (OJ C 269, 23.07.2016, p. 31). Council conclusions on access to medicines and medical devices for a stronger and resilient EU, 2021/C 269 I/02 (OJ C 269I, 7.7.2021, p. 3).

2 European Parliament resolution of 2 March 2017 on EU options for improving access to medicine (2016/2057(INI), European Parliament resolution of 17 September 2020 on the shortage of medicines – how to address an emerging problem (2020/2071(INI).

3 Communication from the Commission, *Pharmaceutical Strategy for Europe* (COM/2020/761 final), https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe_en.

4 Mission letter of the President of the European Commission to Stella Kyriakides, Commissioner for Health and Food Safety, mission-letter-stella-kyriakides_en.pdf (europa.eu)

in advance of a foreseen interruption to continued supply of a medicinal product to the market. To support the sector's global competitiveness and innovative power, right balance needs to be struck between giving incentives for innovation, with more focus on unmet medical needs, and measures on access and affordability.

The framework needs to be simplified, adapted to scientific and technological changes, and contribute to reducing the environmental impact of medicinal products. This proposed reform is comprehensive but targeted and focuses on provisions relevant to achieving its specific objectives; therefore it covers all provisions apart from those concerning advertising, falsified medicinal products, and homeopathic and traditional herbal medicinal products.

Therefore, the objectives of the proposal are the following:

General objectives

– guarantee a high level of public health by ensuring the quality, safety and efficacy of medicinal products for EU patients;

– harmonise the internal market for the supervision and control of medicinal products and the rights and duties incumbent upon the competent authorities of the Member States.

Specific objectives

– make sure all patients across the EU have timely and equitable access to safe, effective, and affordable medicines;

– enhance security of supply and ensure medicines are always available to patients, regardless of where they live in the EU;

– offer an attractive innovation-and competitiveness friendly environment for research, development, and production of medicines in Europe;

– make medicines more environmentally sustainable.

All the general and specific objectives set out above are also relevant for the areas of medicinal products for rare diseases and for children.

• **Consistency with existing provisions in the policy area**

The current EU pharmaceutical legislation includes both general and specific legislation. Directive 2001/83/EC of the European Parliament and of the Council[5] and Regulation (EC) No 726/2004 of the European Parliament and of the Council[6] (together 'general pharmaceutical legislation') lay down provisions related to medicinal products authorisation and post-authorisation requirements, pre-authorisation support schemes, regulatory incentives in terms of data and market protection, manufacturing and supply, and the European Medicines Agency (EMA). The general pharmaceutical legislation is complemented by specific legislation on medicinal products for rare diseases (Regulation (EC) No 141/2000, the 'Orphan

5 Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, p. 67).

6 Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ L 136, 30.4.2004, p. 1).

Regulation'[7]), medicinal products for children (Regulation (EC) No 1901/2006, the 'Paediatric Regulation'[8]) and advanced therapy medicinal products (Regulation (EC) No 1394/2007, the 'ATMP Regulation'[9]). The proposed revision of the pharmaceutical legislation will consist of two legislative proposals:

– a new directive, repealing and replacing Directive 2001/83/EC and Directive 2009/35/EC of the European Parliament and of the Council[10] and incorporating relevant parts of the Paediatric Regulation (Regulation (EC) No 1901/2006)

– a new regulation, repealing and replacing Regulation (EC) No 726/2004, repealing and replacing the Orphan Regulation (Regulation (EC) No 141/2000) and repealing and incorporating relevant parts of the Paediatric Regulation (Regulation (EC) No 1901/2006).

The merger of the Orphan Regulation and the Paediatric Regulation with the legislation applicable to all medicinal products will allow for simplification and increased coherence.

Medicinal products for rare diseases and for children will continue to fall under the same provisions as any other medicinal product concerning their quality, safety and efficacy, for example concerning the marketing authorisation procedures, pharmacovigilance and quality requirements. However, specific requirements will also continue to apply to these types of medicinal products in order to support their development. This is because market forces alone have proven insufficient to stimulate adequate research and development of medicinal products for children and patients suffering from a rare disease. Such requirements, which are currently laid down in separate legislative acts, should be integrated into this regulation and the directive in order to ensure clarity and coherence of all the measures applicable to these products.

• **Consistency with other Union policies**

The EU pharmaceutical legislation described above has close links with several other related pieces of EU legislation. The 'Clinical Trials Regulation' (Regulation (EU) No 536/2014)[11]allows for more efficient approval of clinical trials in the EU. Regulation (EU) 2022/123[12] strengthens the role of the European Medicines Agency in order to facilitate a coordinated EU-level response to health crises. The EMA fees

7 Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products (OJ L 18, 22.1.2000, p. 1).

8 Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 (OJ L 378, 27.12.2006, p. 1).

9 Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (OJ L 324, 10.12.2007, p. 121).

10 Directive 2009/35/EC of the European Parliament and of the Council of 23 April 2009 on the colouring matters which may be added to medicinal products (OJ L 109, 30.4.2009, p. 10).

11 Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (OJ L 158, 27.5.2014, p. 1).

12 Regulation (EU) 2022/123 of the European Parliament and of the Council of 25 January 2022 on a reinforced role for the European Medicines Agency in crisis preparedness and management for medicinal products and medical devices (OJ L 20, 31.1.2022, p. 1).

legislation[13] contributes to providing adequate financing for the EMA's activities, including respective remuneration to national competent authorities for their contribution to completing the EMA's tasks.

There are also links with EU regulatory frameworks for other health products. EU legislation on blood, tissues and cells (BTC)[14] is relevant, as some substances of human origin are starting materials for medicinal products. The EU regulatory framework for medical devices[15] is also relevant, as there are products that combine medicinal products and medical devices.

Futhermore, the objectives of the proposed reform of the pharmaceutical legislation are consistent with those of a number of broader EU policy agendas and initiatives.

In terms of promoting innovation, Horizon Europe[16], a key funding programme for EU research and innovation, and Beating Cancer Plan[17] both support research and development of new medicinal products. In addition, innovation in the pharmaceutical sector is promoted by the intellectual property frameworks, on patents under the national patent laws, the European Patent Convention and the Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement, and on supplementary protection certificates under the EU SPC Regulation[18]. The intellectual property action plan[19] under the Industrial Strategy includes modernising the system of supplementary protection certificates (SPCs). SPCs extend certain patent rights to protect innovation and compensate for lengthy clinical trials and marketing authorisation procedures. With regard to addressing unmet medical needs in the area of antimicrobial resistance, the proposed reform of the pharmaceutical legislation will contribute to the objectives of the European one health action plan against antimicrobial resistance (AMR)[20].

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13 Council Regulation (EC) No 297/95 of 10 February 1995 on fees payable to the European Agency for the Evaluation of Medicinal Products, and Regulation (EU) No 658/2014 of the European Parliament and of the Council on fees payable to the European Medicines Agency for the conduct of pharmacovigilance activities in respect of medicinal products for human use (OJ L 35, 15.2.1995, p. 1).

14 Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC, and Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells(OJ L 033, 8.2.2003, p. 30).

15 Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (OJ L 117, 5.5.2017, p. 1) and Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU (OJ L 117, 5.5.2017, p. 176).

16 Regulation (EU) 2021/695 of the European Parliament and of the Council of 28 April 2021 establishing Horizon Europe – the Framework Programme for Research and Innovation, laying down its rules for participation and dissemination, and repealing Regulations (EU) No 1290/2013 and (EU) No 1291/2013 (OJ L 170, 12.5.2021, p. 1).

17 Communication from the Commission, *Europe's Beating Cancer Plan* (COM/2021/44 final).

18 Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the supplementary protection certificate for medicinal products (OJ L 152, 16.6.2009, p. 1).

19 Communication from the Commission, *Making the most of the EU's innovative potential. An intellectual property action plan to support the EU's recovery and resilience* (COM/2020/760 final).

20 Communication from the Commission, *A European One Health Action Plan against Antimicrobial Resistance (AMR)*, https://ec.europa.eu/health/system/files/2020-01/amr_2017_action-plan_0.pdf.

Concerning access to medicinal products, in addition to the pharmaceutical legislation, the intellectual property frameworks, the Health Technology Assessment (HTA) Regulation (Regulation (EU) 2021/2282)[21] and the Transparency Directive (Directive 89/105/EEC)[22] also play a role. In addition to extending certain patent rights to protect innovation, SPCs impact the effect of regulatory protection periods provided by the pharmaceutical legislation and therefore the entry of generic and biosimilar medicinal products and ultimately patient access to medicinal products and affordability. Under the HTA Regulation, national HTA bodies will conduct joint clinical assessments that compare new medicinal products to existing ones. Such joint clinical assessments will help Member States take more timely and evidence-based decisions on pricing and reimbursement. Finally, the Transparency Directive regulates procedural aspects of the Member States' pricing and reimbursement decisions but does not effect the level of price.

In order to enhance security of supply of medicinal products, the proposed reform of the pharmaceutical legislation aims to address systemic shortages and supply chain challenges. The proposed reform therefore complements and further develops the roles of the Member States and competent authorities of the Member States as set out in the extension of the EMA mandate (Regulation (EU) 2022/123), and is aimed at ensuring access to and continued supply of critical medicinal products during health crises. It also complements the mission of the Health Emergency Preparedness and Response Authority (HERA) to ensure availability of medical countermeasures in preparation for and during health crises. The proposed reform of the pharmaceutical legislation is therefore consistent with the package of legislative initiatives related to health security under the European Health Union[23].

To address environmental challenges, the proposed reform of the pharmaceutical legislation will support initiatives under the European Green Deal[24]. These include the EU action plan 'Towards Zero Pollution for Air, Water and Soil' and the revision of: (i) the Urban Waste Water Treatment Directive[25], (ii) the Industrial Emissions Directive[26] and (iii) the list of surface and groundwater pollutants under the Water Framework Directive[27]. The proposal is also well aligned with the Strategic Approach to Pharmaceuticals in the Environment[28].

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21 Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU (OJ L 458, 22.12.2021, p. 1).

22 Council Directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of national health insurance systems (OJ L 40, 11.2.1989, p. 8).

23 European Health Union - Protecting the health of Europeans and collectively responding to cross-border health crises, https://commission.europa.eu/strategy-and-policy/priorities-2019-2024/promoting-our-european-way-life/european-health-union_en.

24 Communication from the Commission. The European Green Deal. COM(2019) 640 final.

25 Council Directive 91/271/EEC of 21 May 1991 concerning urban waste-water treatment (OJ L 135, 30.5.1991, p. 40).

26 Directive 2010/75/EU of the European Parliament and of the Council of 24 November 2010 on industrial emissions (integrated pollution prevention and control) (OJ L 334 17.12.2010, p. 17).

27 Directive 2000/60/EC of the European Parliament and of the Council of 23 October 2000 establishing a framework for Community action in the field of water policy (OJ L 327, 22.12.2000, p. 1) and Directive 2013/39/EU of the European Parliament and of the Council of 12 August 2013 amending Directives 2000/60/EC and 2008/105/EC as regards priority substances in the field of water policy Text with EEA relevance (OJ L 226, 24.8.2013, p. 1).

28 Strategic Approach to Pharmaceuticals in the Environment,

Finally, on the use of health data, the European Health Data Space[29] will provide a common framework across Member States for access to high-quality real world health data. This will promote progress in research and development of medicinal products and provide new tools for pharmacovigilance and comparative clinical assessments. By facilitating access to and use of health data, the two initiatives together will support the competitiveness and innovation capacity of the EU's pharmaceutical industry.

2. LEGAL BASIS, SUBSIDIARITY AND PROPORTIONALITY

- **Legal basis**

The proposal is based on Articles 114(1) and 168(4), point (c), of the Treaty on the Functioning of the European Union (TFEU). This is consistent with the legal basis of existing EU pharmaceutical legislation. Article 114(1) has as its object the establishment and functioning of the internal market, while Article 168(4), point (c), relates to the setting of high standards for the quality and safety of medicinal products.

- **Subsidiarity (for non-exclusive competence)**

Common standards of quality, safety and efficacy for the authorisation of medicinal products constitute a cross-border public health issue that affects all Member States and thus can be regulated effectively only at EU level. EU action relies also on the single market to achieve a stronger impact as regards access to safe, effective and affordable medicinal products, and with regard to the security of supply across the EU. Uncoordinated measures by Member States may result in distortions of competition and barriers to intra-EU trade for medicinal products that are relevant for the entire EU, and would also likely increase administrative burden for pharmaceutical companies, which often operate in more than one Member State.

A harmonised approach at EU level also provides greater potential for incentives to support innovation and for concerted action to develop medicinal products in areas of unmet medical needs. Moreover, simplification and streamlining of processes under the proposed reform are expected to reduce administrative burden for companies and authorities and hence improve the efficiency and attractiveness of the EU system. The reform will also have a positive influence on the competitive functioning of the market through targeted incentives and other measures that facilitate early market entry of generic and biosimilar medicinal products, contributing to patient access and affordability. Nevertheless, the proposed reform of the pharmaceutical legislation respects Member States' exclusive competence in the provision of health services, including pricing and reimbursement policies and decisions.

- **Proportionality**

The initiative does not go beyond what is necessary to achieve the objectives of the reform. It does so in a way that is conducive to national action, which would otherwise not be sufficient to achieve those objectives in a satisfactory way.

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https://ec.europa.eu/environment/water/water-dangersub/pharmaceuticals.htm.

[29] Communication from the Commission, *A European Health Data Space: harnessing the power of health data for people, patients and innovation* (COM(2022) 196 final).

The principle of proportionality has been reflected in the comparison of different options evaluated in the impact assessment. For example, trade-offs are inherent between the objective of innovation (promoting the development of new medicinal products) and the objective of affordability (which is often achieved by generic/biosimilar competition). The reform maintains the incentives as a key element for innovation, but they are adapted to better encourage and reward product development in areas of unmet medical needs and to better address timely patient access to medicinal products in all Member States.

- **Choice of the instrument**

The proposed regulation introduces a large number of amendments to Regulation (EC) No 726/2004. It also incorporates part of the current provisions and amendments to Regulation (EC) No 1901/2006, as well as current provisions and amendments to Regulation (EC) No 141/2000. A new regulation repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006 (rather than an amending regulation) is therefore considered the appropriate legal instrument.

3. RESULTS OF EX-POST EVALUATIONS, STAKEHOLDER CONSULTATIONS AND IMPACT ASSESSMENTS

- **Ex-post evaluations/fitness checks of existing legislation**

For the reform of the general pharmaceutical legislation, stakeholder consultation activities were carried out as part of the 'back-to-back' evaluations and impact assessments of the general pharmaceutical legislation and of the Orphan and Paediatric Regulations[30].

For medicinal products for rare diseases and for children a joint evaluation on the functioning of the two pieces of legislation was carried out and published in 2020[31].

For the general pharmaceutical legislation the evaluation of the legislation showed that the legislation continues to be relevant for the dual overarching objectives of protecting public health and harmonising the internal market for medicinal products in the EU. The legislation delivered on the objectives of the 2004 revision, albeit not to the same extent for all. The objective of ensuring quality, safety and efficacy of medicinal products was achieved to the largest extent, while patient access to medicinal products in all Member States was achieved only to a limited extent. As to ensuring the competitive functioning of the internal market and attractiveness in a global context, the legislation has performed to a moderate extent. The evaluation found that the achievements or shortcomings of the 2004 revision vis-a-vis its objectives depend on many external factors outside the remit of the legislation. These include R&D activities and international location of R&D clusters, national pricing and reimbursement decisions, business decisions and market size. The pharmaceutical sector and the development of medicinal products are global; research and clinical trials conducted on one continent will support development and authorisation in other continents; global are also the supply chains and manufacturing

30 Commission staff working document, Impact Assessment, Annex 5: Evaluation.

31 Evaluation of the medicines for rare diseases and children legislation, https://health.ec.europa.eu/medicinal-products/medicines-children/evaluation-medicines-rare-diseases-and-children-legislation_en.

of medicinal products. International cooperation to harmonise requirements to support authorisation exists, e.g. the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use[32].

The evaluation identified the main shortcomings that the pharmaceutical legislation has not adequately addressed, while recognising that these also depend on factors outside its remit. These main shortcomings are as follows:

– Medical needs of patients are not sufficiently met.

– Affordability of medicinal products is a challenge for health systems.

– Patients have unequal access to medicinal products across the EU.

– Shortages of medicinal products are an increasing problem in the EU.

– The medicinal product life cycle can have negative impacts on the environment.

– The regulatory system does not sufficiently cater for innovation and in some instances creates unnecessary administrative burden.

Concerning medicinal products for rare diseases and for children, the evaluation showed that overall the two specific pieces of legislation have achieved positive results by allowing more medicinal products to be developed for these two population groups. However, it also identified important shortcomings, which are similar to the ones identified for the general pharmaceutical legislation:

– Medical needs of patients with rare diseases and of children are not sufficiently met.

– Affordability of medicinal products is a growing challenge for health systems.

– Patients have unequal access to medicinal products across the EU.

– The regulatory system does not sufficiently cater for innovation and in some instances creates unnecessary administrative burden.

• **Stakeholder consultations**

For the reform of the general pharmaceutical legislation, stakeholder consultation activities were carried out as part of the 'back-to-back' evaluation and impact assessment[33]. A single consultation strategy was prepared for this exercise, including consultation activities looking backward and forward. It aimed to collect inputs and perspectives of all stakeholder groups both on the evaluation of the legislation and for the impact assessment of different possible policy options for the reform.

The following key stakeholder groups were identified as priority groups in the consultation strategy: the public; organisations representing patients, consumers and civil society active in public health and social issues ('CSOs'); healthcare professionals and healthcare providers; researchers, academia and learned societies (academics); environmental organisations; the pharmaceutical industry and their representatives.

32 ICH – harmonisation for better health, https://www.ich.org/.

33 Commission staff working document, Impact Assessment, Annex 2: Stakeholder Consultation (Synopsis Report).

As part of the internal policy work process supporting the revision, the Commission collaborated with the European Medicines Agency (EMA) and the competent authorities of the Member States (NCAs) dealing with the regulation of medicinal products. Both actors play a pivotal role in implementing the pharmaceutical legislation.

Information was collected through consultations that took place between 30 March 2021 and 25 April 2022. These consisted of:

– feedback on the Commission's combined evaluation roadmap/inception impact assessment (30 March-27 April 2021);

– Commission online public consultation (28 September-21 December 2021);

– targeted stakeholder surveys with public authorities, the pharmaceutical industry including SMEs, academia, civil society representatives and healthcare providers (survey) (16 November 2021-14 January 2022);

– interviews (2 December 2021-31 January 2022);

– a validation workshop on the evaluation findings (workshop-1) on 19 January 2022;

– a validation workshop on the impact assessment findings (workshop 2) on 25 April 2022.

There was broad consensus among stakeholders that the current pharmaceutical system guarantees a high level of patient safety on which the revision can build to address new challenges and improve supply of safe and affordable medicinal products, patient access and innovation, especially in areas where the medical needs of patients are not met. The public, patients and civil society organisations expressed their expectation of equitable access to innovative therapies across the EU, including for unmet medical needs, and continuous supply of their medicinal products. Public authorities and patient organisations opted for a variable duration for the current main incentives, as reflected in the preferred option. The pharmaceutical industry argued against any introduction of variable incentives or the shortening of existing ones and favoured the introduction of additional or novel incentives. Industry also highlighted the need for stability in the current legal framework and predictability for incentives. The elements on the environment, regulatory support for non-commercial entities and repurposing of medicinal products included in the preferred option were supported by key stakeholders such as healthcare providers, academia and environmental organisations.

Concerning the revision of the legislation on medicinal products for children and for rare diseases, specific consultation activities were carried out in the context of the impact assessment procedure: a public consultation ran from 7 May to 30 July 2021. Furthermore, targeted surveys, including a costing survey both for pharmaceutical companies and public authorities, were conducted from 21 June to 30 July 2021 (late responses were accepted until the end of September 2021, due to the summer break). An interview programme with all relevant stakeholder groups (public authorities, pharmaceutical industry including SMEs, academia, civil society representatives and healthcare providers) was conducted at the end of June 2021, while focus groups met on 23 February 2022 to discuss some of the main issue of the revision.

There was broad consensus among stakeholders that the two pieces of legislation have had a positive effect on the development of medicinal products for children and

the treatment of rare diseases. However, concerning the Paediatric Regulation, all the current structure of the paediatric investigation plan and of the condition allowing the waiver of the obligation to draw up such a plan were considered as possible obstacles to the development of certain innovative products. All stakeholders highlighted that for both the medicinal products for rare diseases and the medicinal products for children, medicinal products addressing unmet medical needs of patients should be better supported. Public authorities supported a variable duration for market exclusivity for medicinal products for rare diseases as a tool to better focus development in areas where treatments are not available. The pharmaceutical industry argued any introduction of variable incentives or the shortening of existing ones and favoured the introduction of additional or novel incentives. As for the revision of the general pharmaceutical legislation, industry also highlighted the need for stability in the current legal framework and predictability for incentives.

- **Collection and use of expertise**

In addition to the extensive stakeholder consultation described in previous sections, the following external studies were conducted to support the 'back-to-back' evaluation and impact assessment of the general pharmaceutical legislation and the evaluation and impact assessment of the orphan and paediatric legislation:

– *Study supporting the Evaluation and Impact Assessment of the general pharmaceutical legislation. Evaluation Report*, Technopolis Group (2022).

– *Study supporting the Evaluation and Impact Assessment of the general pharmaceutical legislation. Impact Assessment Report*, Technopolis Group (2022).

– *Future-proofing pharmaceutical legislation - Study on medicine shortages*, Technopolis Group (2021).

– *Study to support the evaluation of the EU Orphan Regulation*, Technopolis Group and Ecorys (2019).

– *Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe*, Copenhagen Economics (2018).

– *Study on the economic impact of the Paediatric Regulation, including its rewards and incentives*, Technopolis Group and Ecorys (2016).

- **Impact assessments**

General pharmaceutical legislation

The impact assessment for the revision of the general pharmaceutical legislation[34] analysed three policy options (A, B and C).

– Option A builds on the status quo and achieves the objectives mainly through new incentives.

– Option B reaches the objectives through more obligations and oversight.

– Option C adopts a 'quid pro quo' approach in the sense that positive behaviour is rewarded and obligations are only used when there are no alternatives.

[34] Commission staff working document, Impact Assessment.

Option A maintains the current system of regulatory protection for innovative medicinal products and adds additional conditional periods of protection. Priority antimicrobials benefit from a transferable exclusivity voucher. Current requirements on security of supply are retained (notification of withdrawal at least 2 months in advance). The existing requirements on the environmental risk assessment continue with additional information obligations.

Option B provides for a variable duration of regulatory data protection periods (split into standard and conditional periods). Companies must either have an antimicrobial in their portfolio or pay into a fund to finance the development of new ones. Companies are obliged to launch medicinal products with an EU-wide authorisation in the majority of Member States (small markets included) and to provide information on public funding received. Current requirements on security of supply are retained and companies are obliged to offer their marketing authorisation for transfer to another company before withdrawal. The environmental risk assessment results in additional responsibilities for companies.

Option C provides for a variable duration of regulatory data protection (split into standard and conditional periods), striking a balance between providing attractive incentives for innovation and supporting timely patient access to medicinal products across the EU. Priority antimicrobials can benefit from a transferable exclusivity voucher subject to strict eligibility criteria and conditions for use of the voucher, while prudent-use measures further contribute to addressing antimicrobial resistance. Marketing authorisation holders are required to ensure transparency on public funding for clinical trials. Reporting of shortages is harmonised and only critical shortages are brought to the attention of authorities at the EU level. Marketing authorisation holders are obliged to notify possible shortages earlier and to offer their marketing authorisation for transfer to another company before withdrawal. Requirements on the environmental risk assessment and conditions of use are strengthened.

All options are complemented by a set of common elements aimed at simplifying and streamlining regulatory procedures and future-proofing the legislation with a view to accommodating novel technologies.

The preferred option is based on option C and also includes the common elements mentioned above. The preferred option was considered to be the best policy choice, taking into account the specific objectives of the reform and the economic, social and environmental impacts of the proposed measures.

The preferred option and its introduction of variable incentives is a cost-effective way of achieving the objectives of improved access, addressing unmet medical need and affordability for health systems. It is expected to provide 8% increased access, meaning 36 million more people residing in the EU who can potentially benefit from a new medicinal product, EUR 337 million in annual gains for public payers, and more medicinal products addressing unmet medical needs. In addition, savings are expected for companies and regulatory authorities through the cross-cutting measures that would allow for better coordination, simplification and accelerated regulatory processes.

Measures to incentivise the development of priority antimicrobials are estimated to entail costs for public payers and the generic industry but could be effective against antimicrobial resistance if applied under strict conditions and with tight measures for prudent use. These costs must also be seen in the context of the threat of resistant

bacteria and current costs incurred from antimicrobial resistance including deaths, healthcare costs and productivity losses. The principal costs for industry are associated with shorter default regulatory data protection period and conditions for extensions of regulatory data protection, and with increased reporting on shortages and environmental risks. Regulatory authorities will incur costs to perform additional tasks in the areas of shortage management, strengthened environmental risk assessment and enhanced pre-authorisation scientific and regulatory support.

Orphan and paediatric legislation

The impact assessment on the revising of the *orphan* and *paediatric* legislation also analysed three policy options (A, B and C) per legislative act. The different policy options vary as to the incentives or rewards to which medicinal products for rare diseases and for children would be entitled. In addition, the revision will include a series of common elements present in all options.

For medicinal products for *rare diseases*, option A keeps the 10 years of market exclusivity and adds - as an additional incentive - a transferable regulatory protection voucher for products addressing a high unmet medical need (HUMN) of patients. Such a voucher allows for a one-year extension in the length of regulatory protection or can be sold to another company and used for a product in that company's portfolio.

Option B abolishes the current market exclusivity of 10 years for all orphan medicinal products.

Option C provides for a variable duration of market exclusivity of 10, 9 and 5 years, based on the type of orphan medicinal product (for HUMN, new active substances and well-established use applications respectively). A 'bonus' market exclusivity extension of 1 year can be granted, based on patient accessibility in all relevant Member States, but only for HUMN products and new active substances.

All options are complemented by a set of common elements aimed at simplifying and streamlining regulatory procedures and future-proofing the legislation.

Option C was considered to be the best policy choice, taking into account the specific objectives and the economic and social impacts of the proposed measures. This option is expected to provide a balanced positive outcome contributing to the achievement of the four objectives of the revision. It will aim to refocus investments and boost innovation, in particular in products addressing HUMN, without undermining the development of other medicinal products for rare diseases. The measures provided for under this option are also expected to improve the competitiveness of EU pharmaceutical industry, including of SMEs, and will lead to the best results in terms of patient access (due to: (i) the possibility for generics and biosimilars to enter the market earlier than they do today; and (ii) the proposed access conditionality for extending the market exclusivity). Furthermore, more flexible criteria to better define an orphan condition will make the legislation more 'fit' to accommodate new technologies and reduce administrative burdens.

The total balance of yearly costs and benefit calculated per interested stakeholder group for this preferred option compared to the baseline are: EUR 662 million cost savings for public payers from accelerated generic entry and a EUR 88 million profit gain for the generic industry. The public will benefit from additional 1 or 2 HUMN medicinal products and overall broader and faster access for patients. Originators will see an estimated EUR 640 million gross profit loss from earlier generic entry,

but savings are expected for companies through the cross-cutting measures in the general pharmaceutical legislation that would allow for better coordination, simplification and accelerated regulatory processes.

For medicinal products *for children*, in option A the 6-month supplementary protection certificate (SPC) extension is kept as a reward for all medicinal products completing a paediatric investigation plan ('PIP'). Furthermore, an extra reward benefiting products addressing unmet medical needs of children is added. This will consist of either 12 extra months of SPC extension or a regulatory protection voucher (duration 1 year), which could be transferred to another product (possibly of another company) against payment, allowing the receiving product to benefit from extended regulatory data protection (+1 year). In option B, the reward for completing a PIP is abolished. Developers of every new medicinal product would continue to be obliged to agree with the EMA and conduct a PIP, but the extra costs incurred would not be rewarded. In option C, like today, the 6-month SPC extension remains the main reward for completing a PIP. All options are complemented by a set of common elements aimed at simplifying and streamlining regulatory procedures and future-proofing the legislation.

Option C was considered the best policy choice, taking into account the proposed measures' specific objectives and economics and social impacts. Option C is expected to yield to an increased number of medicinal products, in particular in areas of unmet medical needs of children, which are expected to reach children faster than today. It would also ensure a fair return of investment for medicinal products developers who fulfil the legal obligation to study medicinal products in children, as well as reduced administrative costs linked to the procedures that follow from the obligation.

New simplification measures and obligations (for example those linked to medicinal product's mechanism of action) are expected to cut time to access to children's versions of medicinal products by 2-3 years and to bring three more new medicinal products for children yearly compared to the baseline, which in turn results in additional rewards for developers. These new medicinal products for children will result, on a yearly basis, in costs for the public estimated EUR 151 million, while originator companies would gain EUR 103 million in gross profits to compensate their efforts. Thanks to simplification of the rewards scheme linked to the study of medicinal products for use in children, generic companies will find it easier to predict when they will be able to enter the market.

- **Regulatory fitness and simplification**

The proposed revisions aim to simplify the regulatory framework and improve its effectiveness and efficiency, thereby reducing the administrative costs borne by companies and competent authorities. Most of the envisaged measures will act on core procedures for the authorisation and life cycle management of medicinal products.

Administrative costs will fall for competent authorities, business and other relevant entities, for two overarching reasons. Firstly, procedures will be streamlined and accelerated, for example in connection with the renewal of marketing authorisations and the submission of variations or the transfer of the responsibility for orphan designations from the Commission to the EMA. Secondly, there will be enhanced coordination of the European medicines regulatory network, for example in terms of the work of different EMA committees and interactions with related regulatory

frameworks. Further contributions to cost reductions for business and administrations are expected to come from adaptations to accommodate new concepts such as adaptive clinical trials, a medicinal product's mechanism of action, use of real world evidence, and new uses of health data within the regulatory framework.

Enhanced digitisation will facilitate the integration of regulatory systems and platforms across the EU and support for the re-use of data, and is expected to reduce costs for administrations over time (although it may induce initial one-off costs). For example, electronic submissions by industry to the European Medicines Agency and competent authorities of the Member States will deliver cost savings to industry. Moreover, the envisaged use of the electronic product information (as opposed to paper leaflets) should also lead to administrative cost reductions.

SMEs and non-commercial entities involved in the development of medicinal products are expected to benefit in particular from the envisaged simplification of procedures, wider use of electronic processes and reduction of administrative burden. The proposal also aims at optimising the regulatory support (e.g. scientific advice) to SMEs and non-commercial organisations, resulting in additional reductions of administrative costs for these parties.

Overall, the envisaged measures for simplification and burden reduction are expected to reduce costs for businesses, supporting the 'one in one out' approach. In particular, the proposed streamlining procedures and enhanced support are expected to yield cost savings for EU pharmaceuticalindustry.

- **Fundamental rights**

The proposal contributes to achieving a high level of human health protection and is therefore consistent with Article 35 of the Charter of Fundamental Rights of the European Union.

4. BUDGETARY IMPLICATIONS

The budgetary implications are set out in the legislative financial statement attached to the proposal.

Budgetary implications are mainly related to additional tasks to be carried out by the European Medicines Agency in terms of providing scientific, administrative and IT support in the following main areas:

– enhanced pre-authorisation scientific and regulatory support;

– decision-making on orphan designations and management of the Union Register of designated orphan medicinal products;

– active substance master file assessment and certification;

– inspection capacities for inspections in third countries and support to Member States;

– environmental risk assessment strengthening;

– shortage management and security of supply.

5. OTHER ELEMENTS

- **Implementation plans and monitoring, evaluation and reporting arrangements**

The development of new medicinal products can be a long process that can take up to 10-15 years. Incentives and rewards therefore have an influence many years after the marketing authorisation date. The benefit for patients also needs to be measured over a period of at least 5-10 years after a medicinal product is authorised. The Commission intends to monitor relevant parameters that enable assessment of progress of the proposed measures with a view to reaching their objectives. The majority of indicators are already collected at the EMA level. Furthermore, the Pharmaceutical Committee[35] will provide a forum for discussing issues related to the transposition and monitoring progress. The Commission will report on the monitoring periodically. A meaningful evaluation of the results of the revised legislation can only be envisaged after at least 15 years from its entry into application.

- **Detailed explanation of the specific provisions of the proposal**

The proposed revision of the pharmaceuticals legislation consists of a proposal for a new regulation and a proposal for a new directive (see previous section 'Consistency with existing provisions in the policy area'), which will also cover orphan and paediatric medicinal products. Provisions for orphan medicinal products have been integrated in the proposed regulation. For paediatric medicinal products, procedural requirements applicable to these products are primarily integrated in the proposed regulation, while the general framework for the authorisation and rewarding of these products has been included in the new directive. The main areas of revision under the proposed new directive are covered by the explanatory memorandum for the accompanying proposal for a directive.

The proposed regulation includes the following main areas of revision:

Promoting innovation and access to affordable medicines creating a balanced pharmaceutical ecosystem

To enable innovation and promote the competitiveness of the EU pharmaceutical industry, in particular small and medium-sized firms, the provisions of the proposed regulation work in synergy with those of the proposed directive.

In this respect, a balanced system of incentives is proposed. The system rewards innovation, especially in areas of unmet medical need, and innovation reaches patients and improves access across the EU, including for medicines for rare diseases. To make the regulatory system more efficient and innovation-friendly, measures are proposed to simplify and streamline procedures and to create an agile and future-proof framework (see the measures proposed further below under '*Reducing regulatory burden and providing a flexible regulatory framework to support innovation and competitiveness'* and in the proposed directive).

Modulation of the length of the market exclusivity for orphan medicinal products

The proposed regulation continues to provide measures to promote research, development and authorisation for medicinal products to address the unmet medical needs of people living with rare diseases, and it targets more those areas of high

[35] Council Decision of 20 May 1975 setting up a pharmaceutical committee (75/320/EEC).

unmet medical needs (HUMN), where research is most needed and investment is riskier. Criteria to identify medicinal products addressing HUMN are set out in the regulation. The duration of market exclusivity is set at [nine] years, except for: (i) orphan medicinal products addressing HUMN, which will get [ten] years, and (ii) well-established use orphan medicinal products, which will be granted [five] years of market exclusivity. A 'bonus' market exclusivity extension of [one] year can be granted, based on patient access in all relevant Member States.

To continue supporting further development of an already authorised orphan medicinal product, while avoiding ever-greening, the first two new indications of an orphan medicinal product will be rewarded with [one] year of exclusivity each. The extension will apply to the entire medicinal product.

Therefore, the modulation of market exclusivity, while keeping the orphan medicinal products reward system very competitive compared to other regions, will better reward medicinal products that will address diseases for which no treatment is available or medicinal products that will bring exceptional advances in treatment. Furthermore, the new system will also promote faster generic/biosimilar competition improving affordability and patient access to orphan medicinal products.

Paediatric investigation plans for medicinal products for children, based on a medicinal product's mechanism of action

Currently, the obligation to conduct a paediatric investigation plan (PIP) for studies in children is waived in certain situations, for example when an adult product is intended for a disease not existing in children. However, in certain cases the molecule in question, due to its molecular mechanism of action, may be efficacious against a disease in children that is different from the one for which it was initially designed for use in adults.

The proposal envisages that in such cases, the product will have to be studied for use in children too. This requirement, apart from increasing the number of medicinal products adequately studied for use in children, is also expected to promote innovation and research.

Measures related to antimicrobials

To promote the development of priority antimicrobials that can address antimicrobial resistance, transferable data exclusivity vouchers are introduced. To this end, strict criteria are laid down for defining the categories of priority antimicrobials eligible to receive the voucher.

Such a voucher will grant an additional year of regulatory data protection to the developer of the priority antimicrobial, which the developer can either use for any product in their own product portfolio or sell it to another marketing authorisation holder.

The number of vouchers will be limited to a maximum of 10 over a 15 year period. Transparency regarding any contribution to the research & development costs for priority antimicrobials will be ensured. Strict conditions are also introduced for the transfer and use of the voucher to extend the data protection period of another product within a certain period, to ensure predictability for competitor products, including generics and biosimilars.

Eligibility criteria and the validity of the voucher are also linked to obligations to supply the priority antimicrobial in the EU. A sunset period of 15 years is proposed,

after which time the Parliament and the Council may decide to continue or review the measure, following a proposal by the Commission, based on experience gained during this period.

Antimicrobial prudent use measures require that antimicrobials are placed under prescription status in the EU. Antimicrobial marketing authorisation holders are required to develop a stewardship plan for antimicrobial resistance which includes information on risk mitigation measures, monitoring and reporting of resistance to the medicinal product.

The environmental fate of the antimicrobial, including through its manufacture and disposal, becomes a factor to be assessed in the environmental risk assessment. The proposal reinforces its provisions on package sizes, educational measures and proper disposal of unused and expired antimicrobials.

Enhanced pre-authorisation scientific and regulatory support

Scientific and regulatory support by the European Medicines Agency will be strengthened, in particular for developers of medicinal products that address unmet medical needs, e.g. by building on the experience gained with the PRIME scheme and procedures used during the COVID-19 pandemic, such as a phased review of data. It will provide an enhanced legal framework for such scientific support and accelerated assessment and authorisation of medicinal products that offer an exceptional therapeutic advancement in areas of unmet medical needs including orphan medicinal products in particular for HUMN.

Small and medium-sized firms and not-for-profit entities will benefit from a dedicated support scheme composed of regulatory, procedural and administrative support, which will also include a reduction, deferral or waiver of fees. In addition, the regulation facilitates the translation of robust research results, carried out by not-for-profit entities, onto the label, allowing new promising therapeutic indications of off-patent medicinal products for unmet medical needs.

Moreover, the European Medicines Agency will be able to provide scientific advice to developers in parallel with the scientific advice given by HTA bodies under the ‘HTA Regulation’ or by expert panels under the ‘Medical Device Regulation’. The European Medicines Agency will also be able to consult other relevant Member State authorities (e.g. with clinical trial expertise) in its scientific advice activities.

These measures are designed to help medicine developers generate clinical evidence that meets the needs of the different authorities along the medicinal products’ life cycle, while respecting the different remits of the legal frameworks concerned.

In addition, the European Medicines Agency will be able to provide scientific opinions related to the classification of products, thereby advising developers and regulators on whether a particular product under development is a medicinal product or not.

Finally, the European Medicines Agency will coordinate a mechanism for consulting public authorities active along the medicinal product life cycle, to promote the sharing of information and the pooling of knowledge on general issues of scientific or technical nature that are relevant for developing, evaluating and accessing medicinal products.

Temporary emergency marketing authorisation

In a public health emergency, it is of major interest for the EU that safe and efficacious medicinal products can be developed and made available within the EU as soon as possible. Agile, fast and simplified processes are of the essence. A range of measures already exist at EU level to facilitate, support and speed up the development of and marketing authorisation for treatments and vaccines during a public health emergency.

The proposed regulation introduces the possibility to grant temporary emergency marketing authorisations to address public health emergencies. Such authorisations should be granted provided that the benefit of the immediate availability of the medicinal product in question on the market, with regard to the circumstances of the public health emergency, outweighs the risk inherent in the fact that additional comprehensive quality, non-clinical, clinical data may not yet be available (though they should still be required at a later stage).

Improving security of supply of medicines

Addressing shortages of medicines

The proposal sets out a framework for the activities to be deployed by the Member States and the Agency to improve the EU's capacity to react efficiently and in a coordinated manner to support shortage management and security of supply of medicinal products, in particular critical medicinal products, to EU citizens, at all times. The provisions to strengthen the security of supply of medicines in the EU were, in part, informed by a structured dialogue with and between the actors in the pharmaceuticals manufacturing value chain and public authorities.

This proposal complements and further develops the core tasks already given to the Agency in the extension of its mandate (Regulation (EU) 2022/123) which was introduced as part of the EU's overall health response to the COVID-19 pandemic and the improved crisis management framework. It also complements Health Emergency Preparedness and Response Authority's (HERA) mission to ensure availability of medical countermeasures in preparation for and during crises.

EMA capacity to inspect sites located in non-EU countries

Challenges in inspection capacity and capability in the EU network have been evident and these gaps have been further exacerbated because of the COVID-19 pandemic. In some cases, the lack of resources has led to delayed inspections of EU interest. Solutions are needed to promote and support extra inspection capacity and build inspector capability, to strengthen the oversight of compliance with good practice by sites located outside the EU. Changes to the legal framework will allow the European Medicines Agency to have the necessary authority and expertise to conduct certain inspections of EU interest also in emergency situations, and when specific capacity and expertise is required.

Joint Audit Programme

To maintain an equivalent and harmonized implementation of the EU legislation on good manufacturing, clinical and distribution practices, and the corresponding enforcement activities, the new legal framework establishes, within the EMA, the Joint Audit Programme (JAP) to ensure that the Member States' inspectorates are subject to regular audits conducted by other Member States.

Furthermore, the JAP will be an essential tool for mutual recognition agreements and other international agreements, as it gives evidence of a regulatory system for

medicinal products based on a network of EU agencies that operate to consistent best practice standards.

Reducing regulatory burden and providing a flexible regulatory framework to support innovation and competitiveness

Improved structure and governance of EMA and the regulatory network

The agility of the European regulatory system is a key component for attracting applicants and developers of medicinal products, from generics and biosimilars to cutting edge medicines. The evaluation and assessment of medicinal products in the EU relies on the EMA, competent authorities of the Member States and their experts who are present in the scientific committees of the EMA.

Both EMA scientific committees and competent authorities of the Member States are faced with an increasing number of procedures, which require additional resources to ensure that rapporteurs and assessors continue to be available to conduct assessment within the appropriate timeframe. Moreover, new challenges arise from the assessment of innovative and complex medicinal products. Capacity limitations that were observed during the COVID-19 pandemic risk becoming more frequent.

It is therefore essential to continue to optimise the functioning and efficiency of the regulatory system. In this regard, duplication of work needs to be avoided and procedures should be handled in the most efficient way.

However, the current structure of the EMA means that in some cases up to five scientific committees are involved in assessing a single medicinal product. Therefore, the structure of the EMA scientific committees is simplified and reduced to two main Committees: the Committee for Medicinal Products for Human Use (CHMP) and the Pharmacovigilance Risk Assessment Committee (PRAC) as the main safety committee.

The expertise of the Committee for Advanced Therapies (CAT), the Committee for Orphan Medicinal Products (COMP), the Paediatric Committee (PDCO) and the Committee for Herbal Medicinal Products (HMPC) will be retained and reorganised in the form of working parties and a pool of experts who will give input to the CHMP, PRAC and the Co-ordination Group for Mutual Recognition and Decentralised Procedures -Human (CMDh).

The CHMP and PRAC will consist, like today, of experts from all Member States, and especially in the CHMP, the voice of patients will be strengthened by appointing patient representatives to this committee for the first time.

Working parties will support the work of the committees and will mostly consist of experts appointed by the Member States based on their expertise and of external experts. This will ensure a continuous link between the experts in the competent authorities of the Member States and the EMA. The model of rapporteurs remains unchanged.

Representation of patients and health care professionals with expertise in all areas, including rare and paediatric diseases, will be increased at the CHMP and PRAC, in addition to the dedicated working parties that represent patients and health care professionals.

This simplified structure is expected to free up resources for the network to focus on new activities, in particular regarding early scientific support for promising

medicinal products and repurposing, as well as activities related to more of a life cycle approach to authorising medicinal products.

Training opportunities will be provided so that all Member States build expertise in new areas of science and technology, so they can actively contribute to the work of the regulatory network in assessing and monitoring medicinal products, including cutting edge innovative and complex medicinal products.

Responsibility for adopting decisions on orphan designations will be transferred from the Commission to the Agency to provide a more effective and efficient procedure.

Other simplification, streamlining and future proofing measures

Reduction of the regulatory burden will be facilitated by measures to simplify regulatory procedures and increased digitalisation, including provisions related to the electronic submission of applications for marketing authorisation and electronic product information (ePI) on authorised medicinal products.

Among the measures to reduce the regulatory burden are the abolishment of the renewal and the sunset clause. The simplification of the structure of the scientific committees at the EMA should also reduce the regulatory burden for companies and simplify their interactions with the EMA.

The reduction of administrative burden through simplification and digitalisation measures will benefit in particular small and medium-sized firms and not-for-profit entities involved in the development of medicinal products. Moreover, a number of measures will contribute to ensuring that the regulatory framework will be able to deal with emerging developments in science. This includes provisions related to adapted clinical trials, use of real-world evidence, secondary use of health data and regulatory sandboxes.

A regulatory sandbox can under certain conditions be linked to an adapted framework, tailored to the characteristics or methods inherent to certain, especially novel medicines, without lowering the high standards of quality, safety and efficacy. Measures for adapted frameworks are provided for in the proposed Directive.

Taken together, the various measures in the proposed regulation and directive addressing simplification to support innovation, future proofing and reduction of the regulatory burden will strengthen the competitiveness of the pharmaceutical sector.

Evolutionary and simplified Paediatric Investigation Plans (PIPs)

For certain type of paediatric developments, the necessity to submit and agree with the EMA, at a very early stage, a full clinical development plan for studies in children, is problematic. In certain cases, this obliges developers to make assumptions about the expected results.

This results in the subsequent need to modify the PIP (when a molecule has never been used before, for instance). With the concept of evolutionary PIP, certain types of developments, like molecules used for the first time in humans, will be given the possibility to initially present a high level clinical development plan.

The EMA will agree that this development plan will be completed and new information submitted at precise stages in the development. This will reduce administrative burden and create, where appropriate, a more agile PIP system.

2023/0131 (COD)

Proposal for a

REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, amending Regulation (EC) No 1394/2007 and Regulation (EU) No 536/2014 and repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006

(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on the Functioning of the European Union, and in particular Article 114 and Article 168(4), point (c), thereof,

Having regard to the proposal from the European Commission,

After transmission of the draft legislative act to the national parliaments,

Having regard to the opinion of the European Economic and Social Committee[1],

Having regard to the opinion of the Committee of the Regions[2],

Acting in accordance with the ordinary legislative procedure,

Whereas:

(1) The Union pharmaceutical framework has enabled the authorisation of safe, efficacious and high-quality medicines in the Union, contributing to a high level of public health and a smooth functioning of the internal market of these products.

(2) The Pharmaceutical Strategy for Europe marks a turning point with the addition of further key objectives and by creating a modern framework that makes innovative and established medicinal products available to patients and healthcare systems at affordable prices, while ensuring security of supply and addressing environmental concerns.

(3) Addressing unequal patient access of medicinal products has become a key priority of the Pharmaceutical Strategy for Europe as has been highlighted by the Council and the European Parliament. Member States have called for revised mechanisms and incentives for development of medicinal products tailored to the level of unmet medical need, while ensuring patient access and availability of medicinal products in all Member States.

(4) Previous amendments to the Union pharmaceutical legislation have addressed access to medicinal products by providing for accelerated assessment for marketing authorisation applications or by allowing conditional marketing authorisation for

[1] OJ C , , p. .
[2] OJ C , , p. .

medicinal products for unmet medical need. While these measures accelerated the authorisation of innovative and promising therapies, these medicinal products do not always reach the patient and patients in the Union still have different levels of access to medicines.

(5) The COVID-19 pandemic has spotlighted critical issues which require a reform of the Union pharmaceuticals framework to strengthen its resilience and to ensure that it serves the people under all circumstances.

(6) For the sake of clarity, it is necessary to replace Regulation (EC) No 726/2004 of the European Parliament and of the Council[3] with a new Regulation.

(7) Veterinary medicinal products are governed by Regulation (EU) No 2019/6 of the European Parliament and of the Council[4]. These medicinal products are outside the scope of this Regulation, even if certain provisions regarding the governance and general tasks of the Agency set out in this Regulation apply to these medicinal products. The specific tasks of the Agency in respect to veterinary medicinal products are laid down in Regulation 2019/6 and Regulation 470/2009 of the European Parliament and of the Council[5].

(8) The scope of centrally authorised medicinal products has been adapted to the realities of the market and technological development as well as the need to ensure a centralised assessment for certain categories of medicinal products. In the light of the Commission's report[6] on the experience gained, it has proved necessary to improve the operation of the marketing authorisation procedures for the placing of medicinal products on the Union market and to amend certain administrative aspects of the European Medicines Agency. In addition, the regulatory framework should be adapted to the current market conditions and economic reality, while continuing to safeguard a high level of protection of public health and the environment. The conclusions of that report call for corrections to some of the operating procedures and require adaptations to take account of scientific and technological development. It also emerges from the report that the general principles previously established which govern the centralised marketing authorisation procedure ('centralised procedure') should be maintained.

(9) As to the scope of this Regulation, the authorisation of antimicrobials is, in principle, in the interest of patients' health at Union level and therefore it should be made possible to authorise them at Union level.

(10) With a view to maintain a high-level of scientific evaluation for new medicinal products and medicinal products that will serve the entire Union population, the

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3 Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ L 136, 30.4.2004, p. 1).

4 Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC (OJ L 4, 7.1.2019, p. 43).

5 Regulation (EC) No 470/2009 of the European Parliament and of the Council of 6 May 2009 laying down Community procedures for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin, repealing Council Regulation (EEC) No 2377/90 and amending Directive 2001/82/EC of the European Parliament and of the Council and Regulation (EC) No 726/2004 of the European Parliament and of the Council (OJ L 152, 16.6.2009, p. 1).

6 Report from the Commission to the European Parliament and the Council on the experience acquired with the procedures for authorising and supervising medicinal products for human use, in accordance with the requirements set out in the EU legislation on medicinal products for human use, COM(2021)497 final.

centralised procedure should be mandatory for high-technological medicinal products, particularly those resulting from biotechnological processes, priority antimicrobials, orphan medicinal products, paediatric use medicinal products and any medicinal product that includes an active substances not authorised before the last important change to the scope of the centralised procedure in 2004.

(11) As regards medicinal products for human use, optional access to the centralised procedure should also be foreseen in cases where use of a single procedure produces added value for the patient. The centralised procedure should remain optional for medicinal products which, although not belonging to the categories of products to be authorised by the Union, are nevertheless therapeutically innovative. It is also appropriate to allow access to this procedure for medicinal products which, although not innovative, may be of benefit to society or to patients, including paediatric patients, if they are authorised from the outset at Union level, such as certain medicinal products which can be supplied without a medical prescription. This option may be extended to generic and biosimilar medicinal products authorised by the Union, provided that this in no way undermines either the harmonisation achieved when the reference medicinal product was evaluated or the results of that evaluation. At the same time, to ensure wide availability of generic medicinal products, those medicinal products may be authorised in any case by the competent authorities of the Member States, even if they are based on a centrally authorised reference medicinal product.

(12) The structure and operation of the various bodies making up the Agency should be designed in such a way as to take into account the need to constantly renew scientific expertise, the need for cooperation between Union and national bodies, the need for adequate involvement of civil society, and the future enlargement of the Union. The various bodies of the Agency should establish and develop appropriate contacts with the parties concerned, in particular with representatives of patients and healthcare professionals.

(13) The chief task of the Agency should be to provide Union institutions and Member States with the best possible scientific opinions to enable them to exercise the powers of authorisation and supervision of medicinal products conferred on them by Union legal acts in the field of medicinal products. Marketing authorisation should be granted by the Commission only after a single scientific evaluation procedure addressing the quality, safety and efficacy of high-technology medicinal products has been conducted by the Agency, applying the highest possible standards.

(14) To ensure close cooperation between the Agency and scientists operating in Member States, the composition of the Management Board should be such as to guarantee that the competent authorities of the Member States are closely involved in the overall management of the Union system for authorising medicinal products.

(15) The Agency's budget should be composed of fees and charges paid by the private sector and contributions from the Union budget to implement Union policies and contributions paid from third countries.

(16) Exclusive responsibility for preparing the Agency's opinions on all questions concerning medicinal products for human use should be vested in the Committee for Medicinal Products for Human Use.

(17) The creation of the Agency through Council Regulation (EEC) No 2309/93[7] which was replaced by Regulation (EC) No 726/2004 has made it possible to reinforce the scientific evaluation and monitoring of medicinal products in the Union, in particular through its scientific bodies and committees for which competent authorities of the Member States provide experts and expertise, ensuring a high quality and independent assessment. This Regulation does not establish a new Agency. The Agency mentioned in this Regulation is the Agency established by Regulation (EC) No 726/2004.

(18) The field of activity of the scientific committees should be enlarged and their operating methods and composition modernised. In this regard it is important to ensure patient and healthcare professional representation in the Committee for Human Medicinal Products as it is the main evaluation committee of the Agency for medicinal products for human use.

(19) Scientific advice for future applicants seeking a marketing authorisation should be provided more generally and in greater depth. Similarly, structures allowing the development of advice for companies, in particular small and medium-sized enterprises ('SMEs'), should be put in place.

(20) Promising medicinal products that have the potential to significantly address patients' unmet medical needs should benefit from early and enhanced scientific support. Such support will ultimately help patients benefit from new therapies as early as possible.

(21) In order to allow for advice that is more informative and an exchange of information between different bodies, scientific advice provided by the Agency should sometimes take place in parallel to scientific advice provided by other bodies. This should be the case for the joint scientific consultation carried out by the Member State Coordination Group on Health Technology Assessment foreseen in Regulation (EU) 2021/2282 of the European Parliament and of the Council[8] and, in cases of medicinal products involving a medical device, the consultation of the expert panels as described in Article 106 of Regulation (EU) No 2017/745 of the European Parliament and of the Council[9]. Where parallel scientific advice consultation mechanisms are established under other relevant Union legal acts, a similar mechanism should apply.

(22) It is also necessary to reinforce the role of the scientific committees in such a way as to enable the Agency to participate actively in international scientific dialogue and to develop certain activities that will be necessary, in particular regarding international scientific harmonisation and technical cooperation with the World Health Organization.

(23) Furthermore, without prejudice to the provisions laid down in Regulation (EU) 2019/6, which remain applicable for veterinary medicinal products, in order to create greater legal certainty, it is necessary to define the responsibilities regarding the transparency rules for the Agency's work, to set certain conditions for the marketing of

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7 Council Regulation (EEC) No 1647/2003 of 18 June 2003 amending Regulation (EEC) No 2309/93 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the evaluation of Medicinal Products (OJ L 245, 29.9.2003, p. 19).

8 Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU (OJ L 458, 22.12.2021, p. 1).

9 Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (OJ L 117, 5.5.2017, p. 1).

medicinal products authorised by the Union, to confer on the Agency powers to monitor the distribution of medicinal products authorised by the Union, to carry out inspections together with the Member States in third countries, and to specify the sanctions and the procedures for implementing them in the event of failure to observe the provisions of this Regulation and the conditions contained in the marketing authorisations granted under the procedures it establishes.

(24) In particular, the Agency should be empowered and given the capacity to carry out inspections, where this is in the interest of the Union and where the competent authorities of the Member States request support in carrying out their tasks under revised Directive 2001/83/EC of the European Parliament and of the Council[10]. The interest of the Union may concern situations where, to ensure faster access to medicinal products, challenges with inspections capacities at national level have to be addressed in a timely manner or where a response to a public health emergency or a major event requires immediate action. Providing the Agency with appropriate inspection capacity will also, in the interest of the Union, facilitate the dissemination of best practices, know-how, and improve the oversight of manufacturing of medicinal products worldwide. Following the request from a competent authority of the Member State, the Agency, at its own discretion, can accept to either provide support to the inspections of sites located in the Union or to carry out inspections of sites located in third countries.

(25) In certain cases, shortcomings in Member States' system of supervision and related enforcement activities could risk to substantially hinder the achievement of the objectives of this Regulation and those of revised Directive 2001/83/EC which could even lead to the emergence of risks to public health. To address these challenges, harmonised inspection standards should be ensured through the establishment of a joint audit programme within the Agency. This joint audit programme will also further harmonise the interpretation of good manufacturing and distribution practices on the basis of Union legislative requirements. Moreover, it will support further mutual recognition of inspection outcomes between Member States and with strategic partners. Within the joint audit programme, the competent authorities are subject to regular audits conducted by other Member States to maintain an equivalent and harmonised quality system and to ensure an appropriate implementation of relevant good manufacturing and distribution practices into national laws and equivalence with other EEA inspectorates.

(26) An inspection working group, which provides input and recommendations on all matters relating, directly or indirectly, to good manufacturing practice and good distribution practice irrespective of the marketing authorisation procedure through different reporting lines, should be established within the Agency. In particular, that working group should be responsible for the establishment, development and overall supervision of the joint audit programme.

(27) To promote innovation and the development of new medicinal products by SMEs within the meaning of Commission Recommendation 2003/361/EC[11], and to reduce the cost of the placing on the market of medicinal products for human use authorised

[10] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, p. 67).

[11] Commission Recommendation of 6 May 2003 concerning the definition of micro, small and medium-sized enterprises (OJ L 124, 20.5.2003, p. 36).

via the centralised procedure, these undertakings should benefit from a support scheme from the Agency.

(28) The support scheme should be composed of regulatory, procedural and administrative support, and of a reduction, deferral or waiver of fees. The scheme should cover the various steps involved in pre-authorisation procedures, such as scientific advice, the submission of the marketing authorisation application, and post-authorisation procedures.

(29) Legal entities that are not engaged in an economic activity such as universities, public bodies, research centres or not-for-profit organisations, represent an important source of innovation and should also benefit from this support scheme. Whereas it should be possible to take account of the particular situation of these entities on an individual basis, such support can best be achieved by means of a dedicated support scheme, including administrative support and through the reduction, deferral and waiver of fees.

(30) The Agency should be empowered to give scientific recommendations on whether a product under development, which could potentially fall under the mandatory scope of the centralised procedure, meets the scientific criteria to be a medicinal product. Such an advisory mechanism would address, as early as possible, questions related to borderline cases with other areas such as substances of human origin, cosmetics or medical devices, which may arise as science develops. To ensure that recommendations given by the Agency take into account the views of equivalent advisory mechanisms in other legal frameworks, the Agency should consult the relevant advisory or regulatory bodies.

(31) To increase transparency of scientific assessments and all other activities, a European medicines web-portal should be created and maintained by the Agency.

(32) Experience with the functioning of the regulatory system has shown that the existing European Medicines Agency multi-scientific committee structure often creates complexity in the scientific assessment process among committees, duplication of work and non-optimised use of expertise and resources. In addition, the Agency and the competent authorities of the Member States are confronted with challenges related to limited capacity and appropriate expertise to deal with increasing number of procedures related to existing medicinal products and assessment of new ones, in particular cutting edge innovative and complex medicinal products.

(33) To optimise the functioning and efficiency of the regulatory system, the structure of the Agency's scientific committees is simplified and reduced to two main Committees for medicinal products for human use, the Committee for Medicinal Products for Human Use (CHMP) and Pharmacovigilance Risk Assessment Committee (PRAC).

(34) The simplification of procedures should not have an impact on standards or the quality of scientific evaluation of the medicinal products to guarantee the quality, safety and efficacy of medicinal products. It should also allow for the reduction of the scientific evaluation period from 210 days to 180 days.

(35) The Agency's scientific committees should be able to delegate some of their evaluation duties to working parties which should be open to experts from the scientific world and appointed for this purpose, whilst retaining complete responsibility for the scientific opinions issued by them.

(36) The expertise of the Committee for Advanced Therapies (CAT), the Committee for Orphan Medicinal Products (COMP), the Paediatric Committee (PDCO) and

Committee for Herbal Medicinal Products (HMPC) is retained through working groups, working parties and a pool of experts who are organised based on different domains and who are giving input to the CHMP and PRAC. The CHMP and PRAC consists of experts from all Member States while working parties consist in majority of experts appointed by the Member States, based on their expertise, and of external experts. The model of rapporteurs remains unchanged. Representation of patients and health care professionals, with expertise in all areas, including rare and paediatric diseases, is increased at the CHMP and PRAC, in addition to the dedicated working groups representing patients and health care professionals.

(37) Scientific committees like the CAT have been instrumental to ensure expertise and capacity building in an emerging technological field. However, after more than 15 years, advanced therapy medicinal products are now more common. The full integration of their assessment in the work of the CHMP will facilitate the assessment of medicinal products within the same therapeutic class, independent of the technology on which they are based. It will also ensure that all biological medicinal products are assessed by the same committee.

(38) To allow for more informative advice on clinical trial applications and therefore a more integrated development advice in view of future data requirements for marketing authorisation applications, the Agency can engage in consultation with representatives from Member States with clinical trial expertise. Nevertheless, decisions on clinical trial applications should remain within the competence of the Member States, in accordance with Regulation (EU) No 536/2014 of the European Parliament and of the Council[12].

(39) To allow for a more informative decision making and for exchange of information and pooling of knowledge on general issues of scientific or technical nature related to the tasks of the Agency regarding medicinal products for human use, in particular to scientific guidelines on unmet medical needs and the design of clinical trials, or other studies and the generation of evidence along the life cycle of medicinal product, the Agency should be able to have recourse to a consultation process of authorities or bodies active along the life cycle of medicinal products. These authorities could be, as appropriate, representatives from Heads of Medicines Agencies, the Clinical Trial Coordination and Advisory Group, the SoHO Coordination Board, the Coordination Group on Health Technology Assessment, Medical Devices Coordination Group, medical devices national competent authorities, national competent authorities for pricing and reimbursement of medicines, national insurance funds or healthcare payers. The Agency should also be able to extend the consultation mechanism to consumers, patients, healthcare professionals, industry, associations representing payers, or other stakeholders, as relevant.

(40) Member States should ensure adequate funding of competent authorities to carry out their tasks under this Regulation and under [revised Directive 2001/83/EC]. In addition, in line with the Joint Statement of the European Parliament, the Council of the EU and the European Commission on decentralised agencies[13], Member States should ensure adequate resources are assigned by the competent authorities of the

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12 Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (OJ L 158, 27.5.2014, p. 1).

13 https://europa.eu/european-union/sites/europaeu/files/docs/body/joint_statement_and_common_approach_2012_en.pdf

Member States for the purpose of their contributions to the work of the Agency, taking into account the cost-based remuneration they receive from the Agency.

(41) In the context of cooperation with international organisations to support global public health, it is important to leverage the scientific assessment performed by the Union and to promote reliance by third country regulatory authorities based on the use of certificates of medicinal products for authorised medicinal products in the Union. An applicant may request independently or as part of an application under the centralised procedure a scientific opinion from the Agency for the use of the medicinal product for markets outside the Union. The Agency should cooperate with the World Health Organization and relevant third country regulatory authorities and bodies to issue such scientific opinions.

(42) The Agency may cooperate with competent authorities of third countries in the context of performing its tasks. Such regulatory cooperation should be coherent with the broader economic relationship of the Union with the third country concerned, taking account of the relevant international agreements between the Union and that third country.

(43) In the interest of public health, marketing authorisation decisions under the centralised procedure should be taken on the basis of the objective scientific criteria of quality, safety and efficacy of the medicinal product concerned, to the exclusion of economic and other considerations. However, Member States should be able, exceptionally, to prohibit the use in their territory of medicinal products for human use.

(44) The quality, safety and efficacy criteria of [revised Directive 2001/83/EC] should apply to medicinal products authorised by the Union under the centralised procedure. The benefit-risk balance of all medicinal products will be assessed when they are placed on the market, and at any other time the competent authority deems appropriate.

(45) Marketing authorisation applications, like any other application submitted to the Agency, should follow the digital by default principle and hence be sent to the Agency in electronic form. Applications should be assessed based on the file submitted by the applicant in accordance with the different legal basis provided by [revised Directive 2001/83/EC]. At the same time, the Agency and the relevant committees may take into account any information that is in its possession. Applicants shall be requested to generally submit raw data, in particular with regard to the clinical trials performed by the applicant in order to ensure a full assessment of the quality, safety and efficacy of the medicinal product.

(46) Directive 2010/63/EU of the European Parliament and of the Council on the protection of animals used for scientific purposes[14] lays down provisions on the protection of animals used for scientific purposes based on the principles of replacement, reduction and refinement. Any study involving the use of live animals, which provides essential information on the quality, safety and efficacy of a medicinal product, should take into account those principles of replacement, reduction and refinement, where they concern the care and use of live animals for scientific purposes, and should be optimised in order to provide the most satisfactory results whilst using the minimum number of animals. The procedures of such testing should be designed to avoid causing pain,

[14] Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes (OJ L 276, 20.10.2010, p. 33).

suffering, distress or lasting harm to animals and should follow the available Agency and the International Committee for Harmonisation (ICH) guidelines. In particular, the marketing authorisation applicant and the marketing authorisation holder should take into account the principles laid down in Directive 2010/63/EU, including, where possible, use of new approach methodologies in place of animal testing. These can include but are not limited to: in vitro models, such as microphysiological systems including organ-on-chips, (2D and 3D) cell culture models, organoids and human stem cells-based models; in silico tools or read-across models.

(47) Procedures should be in place to facilitate joint animal testing, wherever possible, in order to avoid unnecessary duplication of testing using live animals covered by Directive 2010/63/EU. Marketing authorisation applicants and marketing authorisation holders should make all efforts to reuse animal study results and make the results obtained from animal studies publicly available. For abridged applications marketing authorisation applicants should refer to the relevant studies conducted for the reference medicinal product.

(48) The summary of product characteristics and the package leaflet should reflect the assessment of the Agency and be part of its scientific opinion. The opinion may recommend certain conditions that should be part of the marketing authorisation, for example on the safe and efficacious use of the medicinal product or on post-authorisation obligations that have to be complied with by the marketing authorisation holder. Those conditions may include the requirement to conduct post-authorisation safety or efficacy studies or other studies that are considered necessary to optimise the treatment, for example where the proposed dose scheme by the applicant, whilst acceptable and justifying a positive benefit-risk balance, could be further optimised post-authorisation. Where the applicant disagrees with parts of the opinion, the applicant may request its re-examination.

(49) Due to the need to reduce overall approval times for medicinal products, the time between the opinion of the Committee for Medicinal Products for Human Use (CHMP) and the final decision on the application for a marketing authorisation should in principle be no longer than 46 days.

(50) On the basis of the opinion of the Agency the Commission should adopt a decision on the application by means of implementing acts. In justified cases, the Commission may return the opinion for further examination or deviate in its decision from the opinion of the Agency. Taking into account the need to make medicinal products swiftly available to patients, it should be acknowledged that the chairperson of the Standing Committee on Medicinal Products for human use will use the available mechanisms under Regulation (EU) 182/2011 of the European Parliament and of the Council[15] and notably the possibility to obtain the committee's opinion by written procedure and within expeditious deadlines which, in principle, will not exceed 10 calendar days.

(51) As a general rule a marketing authorisation should be granted for an unlimited time; however, one renewal may be decided only on justified grounds related to the safety of the medicinal product.

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[15] Regulation (EU) No 182/2011 of the European Parliament and of the Council of 16 February 2011 laying down the rules and general principles concerning mechanisms for control by Member States of the Commission's exercise of implementing powers (OJ L 55, 28.2.2011, p. 13).

(52) There is a need to provide for the ethical requirements of Regulation (EU) No 536/2014 to apply to medicinal products authorised by the Union. In particular, with respect to clinical trials conducted outside the Union on medicinal products destined to be authorised within the Union, at the time of the evaluation of the application for authorisation, it should be verified that these trials were conducted in accordance with the principles equivalent to these of Regulation (EU) No 536/2014 as regards the rights and safety of the subject and the reliability and robustness of the data generated in the clinical trial.

(53) Environmental risks may arise from medicinal products containing or consisting of genetically modified organisms. It is thus necessary to subject such medicinal products to an environmental risk-assessment procedure similar to the procedure under Directive 2001/18/EC of the European Parliament and of the Council[16], to be conducted in parallel with the evaluation, under a single Union procedure, of the quality, safety and efficacy of the medicinal product concerned. The environmental risk-assessment should be conducted in accordance with the requirements set out in this Regulation and in [revised Directive 2001/83/EC] which are based on the principles set out in Directive 2001/18/EC but taking into account the specificities of medicinal products.

(54) [revised Directive 2001/83/EC] permits Member States to temporarily allow the use and supply of unauthorised medicinal products for public health reasons or individual patient needs and that includes medicinal products to be authorised under this Regulation. It is also necessary, that Member States are allowed under this Regulation to make a medicinal product available for compassionate use prior to its marketing authorisation. In those exceptional and urgent situations, where there is a lack of a suitable authorised medicinal product, the need to protect public health or the health of individual patients must prevail over other considerations, in particular the need to obtain a marketing authorisation and consequently, to have available complete information about the risks posed by the medicinal product, including any risks to the environment from medicinal products containing or consisting of genetically modified organisms (GMOs). To avoid delays in making these products available or uncertainties as regards their status in certain Member States, it is appropriate, in those exceptional and urgent situations, that for a medicinal product containing or consisting of GMOs, an environmental risk assessment or consent in accordance with Directive 2001/18/EC or Directive 2009/41/EC of the European Parliament and of the Council[17] should not be a prerequisite. Nevertheless, in these cases, Member States should implement appropriate measures to minimise foreseeable negative environmental impacts resulting from the intended or unintended release of the medicinal products containing or consisting of GMOs into the environment.

(55) For medicinal products, the period for protection of data relating to non-clinical tests and clinical trials should be the same as that provided for in [revised Directive 2001/83/EC].

(56) In order to meet, in particular, the legitimate expectations of patients and to take account of the increasingly rapid progress of science and therapies, accelerated

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16 Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC (OJ L 106, 17.4.2001, p. 1).

17 Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the contained use of genetically modified micro-organisms (Recast) (OJ L 125, 21.5.2009, p. 75).

assessment procedures should be set up, reserved for medicinal products of major therapeutic interest, and procedures for obtaining conditional marketing authorisations subject to certain regularly reviewable conditions.

(57) Compassionate use programmes allow for an early access to medicinal products. Existing provisions should be reinforced to ensure that a common approach is followed, whenever possible, regarding the criteria and conditions for the compassionate use of new medicinal products under Member States' legislation. Moreover, it is important to allow for data on such uses to be collected to inform decisions regarding the benefit-risk balance of the medicinal products concerned.

(58) There is the possibility under certain circumstances for marketing authorisations to be granted, subject to specific obligations or conditions, on a conditional basis or under exceptional circumstances. The legislation should allow under similar circumstances for medicinal products with a standard marketing authorisation for new indications to be authorised on a conditional basis or under exceptional circumstances. The medicinal products authorised on a conditional basis or under exceptional circumstances should in principle satisfy the requirements for a standard marketing authorisation with the exception of the specific derogations or conditions outlined in the relevant conditional or exceptional marketing authorisation and shall be subject to specific review of the fulfilment of the imposed specific conditions or obligations. It is also understood that the grounds for refusal of a marketing authorisation shall apply *mutatis mutandis* for such cases.

(59) In principle, only one marketing authorisation may be granted to an applicant for a medicinal product. Duplicate marketing authorisations should only be granted in exceptional circumstances. When those exceptional circumstances are no longer present, notably as regards the protection by a patent or a supplementary protection certificate in one or more Member States, any potentially negative effects on markets from the existence of duplicate marketing authorisations should be minimised through a withdrawal of the initial or the duplicate marketing authorisation.

(60) Regulatory decision-making on the development, authorisation and supervision of medicinal products may be supported by access and analysis of health data, including real world data, where appropriate, i.e. health data generated outside of clinical studies. The Agency should be able to use such data, including via the Data Analysis and Real World Interrogation Network (DARWIN) and the European Health Data Space interoperable infrastructure. Through these capabilities the Agency may take advantage of all the potential of supercomputing, artificial intelligence and big data science to fulfil its mandate, without compromising privacy rights. Where necessary the Agency may cooperate with the competent authorities of the Member States towards this objective.

(61) The handling of health data requires a high level of protection against cyber attacks. It is necessary for the Agency to be equipped with a high level of security controls and processes against cyber attacks to ensure that the Agency operates normally at all times. To that end, the Agency should establish a plan to prevent, detect, mitigate and respond to cyber attacks so that its operations are secure at all times, while preventing any illegal access to documentation held by the Agency.

(62) Due to the sensitive nature of health data, the Agency should safeguard its processing operations and ensure that they respect the data protection principles of lawfulness, fairness and transparency, purpose limitation, data minimisation, accuracy, storage limitation, integrity and confidentiality. Where the processing of personal data is

necessary for the purposes of this Regulation, such processing should be done in accordance with Union law on the protection of personal data. Any processing of personal data under this Regulation should take place in accordance with Regulation (EU) 2016/679[18] and Regulation (EU) 2018/1725[19] of the European Parliament and of the Council.

(63) Access to individual patient data from clinical studies in structured format allowing for statistical analyses is valuable to assist regulators in understanding the submitted evidence and to inform regulatory decision-making on the benefit-risk balance of a medicinal product. The introduction of such possibility in the legislation is important to foster data-driven benefit-risk assessments at all stages of the life cycle of a medicinal product. This Regulation therefore empowers the Agency to request such data as part of the assessment of initial and post-authorisation applications.

(64) For generic and biosimilar medicinal products, as a general rule, risk management plans should not be developed and submitted, also considering that the reference medicinal product has such a plan; however, in specific cases, a risk management plan for generic and biosimilar medicinal products should be developed and submitted to the competent authorities.

(65) In the preparation of scientific advice and in duly justified cases, the Agency should also be able to consult authorities established in other relevant Union legal acts or other public bodies established in the Union, as applicable. These may include experts in clinical trials, medical devices, substances of human origin or any other as required for the provision of the scientific advice in question.

(66) Through the Priority Medicines (PRIME) scheme, the Agency has gained experience of the provision of early scientific and regulatory support to developers of certain medicinal products that, based on preliminary evidence, are likely to address an unmet medical need and are considered promising at an early stage of development. It is appropriate to recognise this early support mechanism, including for priority antimicrobials and repurposed medicinal products when they fulfil the criteria for the scheme, and allow the Agency, in consultation with the Member States and the Commission, to establish selection criteria for promising medicinal products.

(67) The Agency, in consultation with the Member States and the Commission, should set the scientific selection criteria for medicinal products that receive pre-authorisation support with priority to be given to the most promising developments in therapies. In the case of medicinal products for unmet medical needs, based on the scientific selection criteria set by the Agency, any interested developer can submit preliminary evidence to demonstrate that the medicinal product has the potential to provide a major therapeutic advancement with respect to the identified unmet medical need.

(68) Before a medicinal product for human use is authorised for placing on the market of one or more Member States, it generally has to undergo extensive studies to ensure

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[18] Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation) (OJ L 119, 4.5.2016, p. 1).

[19] Regulation (EU) 2018/1725 of the European Parliament and of the Council of 23 October 2018 on the protection of natural persons with regard to the processing of personal data by the Union institutions, bodies, offices and agencies and on the free movement of such data, and repealing Regulation (EC) No 45/2001 and Decision No 1247/2002/EC (OJ L 295, 21.11.2018, p. 39).

that it is safe, of high quality and effective for use in the target population. However, in the case of certain categories of medicinal products for human use, in order to meet unmet medical needs of patients and in the interest of public health, it may be necessary to grant marketing authorisation on the basis of less complete data than is normally the case. Such marketing authorisation should be granted subject to specific obligations. The categories of medicinal products for human use concerned should be the medicinal products, including orphan medicinal products, that aim at the treatment, prevention or medical diagnosis of seriously debilitating or life-threatening diseases, or that are intended to be used in emergency situations in response to public health threats.

(69) The Union should have the means to carry out a scientific assessment of the medicinal products presented in accordance with the decentralised marketing authorisation procedures. Moreover, with a view to ensuring the effective harmonisation of administrative decisions taken by Member States with regard to medicinal products presented in accordance with decentralised marketing authorisation procedures, it is necessary to endow the Union with the means to resolve disagreements between Member States concerning the quality, safety and efficacy of medicinal products.

(70) In the event of a risk to public health, the marketing authorisation holder or the competent authorities should be able to make urgent safety or efficacy restrictions on their own initiative to ensure a swift adaption of the marketing authorisation to maintain the safe and efficacious use of the medicinal product by healthcare professionals and patients. If a review is launched on the same safety or efficacy concern addressed by urgent restrictions initiated by a competent authority, any written observations by the marketing authorisation holder should be considered in that review to avoid duplication of assessment.

(71) The terms of a marketing authorisation for a medicinal product for human use may be varied. While the core elements of a variation are laid down in this Regulation, the Commission should be empowered to complement these elements by laying down further necessary elements, to adapt the system to technical and scientific progress, and to employ digitalisation measures to ensure that unnecessary administrative burden is avoided for marketing authorisation holders and competent authorities.

(72) To avoid unnecessary administrative and financial burden both for the pharmaceutical industry and the competent authorities, certain streamlining measures should be introduced. Electronic applications for marketing authorisations and for variations to the terms of the marketing authorisation should be made possible.

(73) To optimise the use of resources for both applicants for marketing authorisations and competent authorities assessing such applications, a single assessment of an active substance master file should be introduced. The outcome of the assessment should be issued through a certificate. To avoid duplication of assessment, the use of an active substance master file certificate should be mandatory for subsequent applications or marketing authorisations for medicinal products for human use containing that active substance from an active substance master file certification holder. The Commission should be empowered to establish the procedure for the single assessment of an active substance master file. To further optimise the use of resources, the Commission should be empowered to extend the certification scheme to additional quality master files, e.g. in case of novel excipients, adjuvants, radiopharmaceutical precursors and active substance intermediates, when the intermediate is a chemical active substance by itself or used in conjugation with a biological substance.

(74) To avoid unnecessary administrative and financial burdens for applicants, marketing authorisation holders and competent authorities, certain streamlining measures should be introduced. Electronic application for marketing authorisation and for variations to the terms of the marketing authorisation should be introduced. For generic and biosimilar medicinal products, except in specific cases, risk management plans do not need to be developed and submitted to the competent authorities.

(75) In a situation of public health emergency, it is of major interest for the Union that safe and efficacious medicinal products can be developed and made available within the Union as soon as possible. Agile, fast and streamlined processes are of the essence. A range of measures already exists at Union level to facilitate, support and speed up the development of and granting marketing authorisations for treatments and vaccines during a public health emergency.

(76) It is considered appropriate to also have the possibility for the Commission to grant temporary emergency marketing authorisations to address public health emergencies. Temporary emergency marketing authorisations may be granted provided that, having regard to the circumstances of the public health emergency, the benefit of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent to the fact that additional comprehensive quality, non-clinical, clinical data may still be required. A temporary emergency marketing authorisation should be valid only during the public health emergency. The Commission should be given the possibility to vary, suspend or revoke such marketing authorisations in order to protect public health or when the marketing authorisation holder has not complied with the conditions and obligations set out in the temporary emergency marketing authorisation.

(77) The development of antimicrobial resistance is a growing concern and the pipeline of effective antimicrobials is obstructed due to a market failure; it is therefore necessary to consider new measures to promote the development of priority antimicrobials that are effective against antimicrobial resistance and to support undertakings, often SMEs, which choose to invest in this area.

(78) To be considered a ‘priority antimicrobial’, a medicinal product should represent a real advancement against antimicrobial resistance and should therefore bring forward non-clinical and clinical data that underpin a significant clinical benefit with respect to antimicrobial resistance. When assessing the conditions for antibiotics, the Agency shall take into account the prioritisation of pathogens as regards the risk of antimicrobial resistance provided for in the ‘WHO priority pathogens list for R&D of new antibiotics’, specifically those listed as priority 1 (critical) or priority 2 (high) or in case there is an equivalent list of priority pathogens adopted at Union level, the Agency should take such Union list into account as a priority.

(79) The creation of a voucher rewarding the development of priority antimicrobials through an additional year of regulatory data protection has the capacity to provide the needed financial support to developers of priority antimicrobials. However, in order to ensure that the financial reward which is ultimately borne by health systems is mostly absorbed by the developer of the priority antimicrobial and not the buyer of the voucher, the number of available vouchers on the market should be kept to a minimum. It is therefore necessary to establish strict conditions of granting, transfer and use of the voucher and to further give the possibility to the Commission to revoke the voucher under certain circumstances.

(80) A transferable data exclusivity voucher should only be available to those antimicrobial products that bring a significant clinical benefit with respect to antimicrobial resistance, and which have the characteristics described in this Regulation. It is also necessary to ensure that an undertaking which receives this incentive is in turn capable to supply the medicinal product to patients across the Union in sufficient quantities and to provide information on all funding received for research related to its development in order to provide a full account of the direct financial support given to the medicinal product.

(81) To ensure a high level of transparency and complete information on the economic effect of the transferable data exclusivity voucher, notably as regards the risk of overcompensation of investment, a developer of a priority antimicrobial is required to provide information on all direct financial support received for research related to the development of the priority antimicrobial. The declaration should include direct financial support received from any source worldwide.

(82) A transfer of a voucher for a priority antimicrobial may be conducted by sale. The value of the transaction which may be monetary or otherwise agreed between the buyer and the seller, shall be made public so as to inform regulators and the public. The identity of the holder of a voucher that has been granted and not yet used should be publicly known at all times so as to ensure a maximum level of transparency and trust.

(83) The provisions related to transferable data exclusivity vouchers shall be applicable for a specified period from the entry into force of this Regulation or until a maximum number of vouchers are granted by the Commission in order to limit the total cost of the measure to Member State health systems. The limited application of the measure will also provide the possibility to assess the effect of the measure in addressing the market failure in the development of new antimicrobials addressing antimicrobial resistance and assess the cost on national health systems. Such assessment will provide the necessary knowledge to decide whether to extend the application of the measure.

(84) The period of application of the provisions on transferable exclusivity vouchers for priority antimicrobials and the total number of vouchers may be extended by the Parliament and the Council upon proposal by the Commission on the basis of the experience acquired.

(85) Where the Commission considers that there are reasons to believe that a medicinal product could present a potential serious risk to human health, a scientific evaluation of the medicinal product should be undertaken by the Agency, leading to a decision whether to maintain, vary, suspend or revoke the marketing authorisation, and taken on the basis of an overall benefit-risk assessment. The Commission may also act on a centralised marketing authorisation where the conditions attached to it are not complied with.

(86) Medicinal products for rare diseases and for children should be subject to the same provisions as any other medicinal product concerning their quality, safety and efficacy, for example for what concerns the marketing authorisation procedures, the pharmacovigilance and quality requirements. However, specific requirements also apply to them. Such requirements, which are currently defined in separate legislations, should be integrated in this Regulation in order to ensure clarity and coherency of all the measures applicable to these medicinal products.

(87) Some orphan conditions occur so infrequently that the cost of developing and bringing to the market a medicinal product to diagnose, prevent or treat the condition cannot be recovered by the expected sales of the medicinal product. However, patients suffering from rare conditions should be entitled to the same quality of treatment as other patients; it is therefore necessary to stimulate the research, development and placing on the market of appropriate medications by the pharmaceutical industry.

(88) Regulation (EC) No 141/2000 of the European Parliament and of the Council[20] has proved to be successful in boosting developments of orphan medicinal products in the Union; therefore an action at Union level remains preferable to uncoordinated measures by the Member States which may result in distortions of competition and barriers to intra-Union trade.

(89) The open and transparent Union procedure for the designation of potential medicinal products as orphan medicinal products established by Regulation (EC) No 141/2000 should be maintained. To increase legal clarity and simplification, the specific legal provisions applicable to these medicinal products should be integrated in this Regulation.

(90) Objective criteria for the orphan designation based on the prevalence of the life-threatening or chronically debilitating condition for which diagnosis, prevention or treatment is sought and the existence of no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Union should be maintained; a prevalence of not more than five affected persons per 10 000 is generally regarded as the appropriate threshold. The orphan designation criterion on the basis of return on investment has been abolished, since it has never been used.

(91) The criterion for orphan designation based on prevalence of a disease may, however, not be appropriate to identify rare diseases in all cases. For example, for conditions which have a short duration and high mortality, measuring the number of people that acquired the disease during a specific time period would better reflect if it is rare within the meaning of this Regulation than measuring the number of people who are 'affected by it' in a specific moment of time. With the aim to better identify only those diseases which are rare, the Commission should be empowered to set up specific designation criteria for certain conditions if the one provided for are not appropriate due to scientific reasons and on the basis of a recommendation of the Agency.

(92) With the aim to better identify only those diseases which are rare, the Commission should be empowered to supplement the designation criteria by a delegated act if they are not appropriate for certain conditions due to scientific reasons and on the recommendation of the Agency. In addition, the designation criteria require implementing measures to be adopted by the Commission.

(93) If a satisfactory method of diagnosis, prevention or treatment of the condition in question has already been authorised in the Union, the orphan medicinal product will have to be of significant benefit to those affected by that condition. In this context, a medicinal product authorised in one Member State is generally deemed as being authorised in the Union. It is not necessary for it to have Union authorisation or to be authorised in all Member States to be considered as a satisfactory method. In addition,

[20] Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products (OJ L 18, 22.1.2000, p. 1).

commonly used methods of diagnosis, prevention or treatment that are not subject to a marketing authorisation may be considered satisfactory if there is scientific evidence of their efficacy and safety. In certain cases, medicinal products prepared for an individual patient in a pharmacy according to a medical prescription, or according to the prescriptions of a pharmacopoeia and intended to be supplied directly to patients served by the pharmacy, may be considered as satisfactory treatment if they are well known and safe and this is a general practice for the relevant patient population in the Union.

(94) The competence to designate a medicinal product as an orphan medicinal product, in the form of a decision, is accorded to the Agency. This is expected to facilitate and expedite the designation procedure, while ensuring high level of scientific expertise.

(95) In order to incite faster authorisation of designated orphan medicinal products, the validity of orphan designation has been set at seven years, with the possibility of extension by the Agency under certain specified conditions; the orphan designation may be withdrawn at the request of the orphan medicine sponsor.

(96) The Agency is responsible for designation of an orphan medicinal product as well as for the setting up and management of a register of designated orphan medicinal products. That register should be publicly available and the minimum data which should be included in the register have been specified in this Regulation with the empowerment for the Commission to amend or supplement this data by a delegated act.

(97) Sponsors of orphan medicinal products designated under this Regulation should be entitled to the full benefit of incentives granted by the Union or by the Member States to support the research and development of medicinal products for the diagnosis, prevention or treatment of such conditions, including rare diseases.

(98) Patients suffering from orphan conditions deserve medicinal products of the same quality, safety and efficacy as other patients; orphan medicinal products should therefore be submitted to the normal evaluation process carried out by the Committee of Medicinal Products for Human Use for the applicant to obtain an marketing authorisation for orphan medicinal product, while a separate marketing authorisation may be granted for indications not fulfilling the criteria of an orphan medicinal product.

(99) A vast percentage of rare diseases remains without treatment with research and development clustered in the areas where profit is better assured. Therefore, there is a need to target those areas where research is mostly needed and where investments are most risky.

(100) Orphan medicinal products addressing a high unmet medical need prevent, diagnose or treat conditions where either no other method of prevention, diagnosis or treatment exists or, if such method already exists, they would bring exceptional therapeutic advancement. In both cases, the criterion of meaningful reduction in disease morbidity or mortality for the relevant patient population should ensure that only most effective medicinal products are covered. The Agency should draw up scientific guidelines on the category of ‘orphan medicinal products addressing a high unmet medical need’.

(101) Experience since the adoption of Regulation (EC) No 141/2000 shows that the strongest incentive for industry to invest in the development and making available of orphan medicinal products is where there is a prospect of obtaining market exclusivity for a certain number of years during which part of the investment might be recovered.

In addition to the periods of market exclusivity, orphan medicinal products will benefit from the periods of regulatory protection set out in [revised Directive 2001/83/EC], including the prolongations of regulatory data protection. However, where an orphan medicinal product obtains an additional therapeutic indication it will benefit only from the prolongation of market exclusivity.(102) In order to incentivise research and development of orphan medicinal products addressing high unmet needs, to ensure market predictability and to ensure a fair distribution of incentives, a modulation of market exclusivity has been introduced; orphan medicinal products addressing high unmet medical needs benefit from the longest market exclusivity, while market exclusivity for well-established use orphan medicinal products, requiring less investment, is the shortest. In order to ensure increased predictability for developers, the possibility to review the eligibility criteria for market exclusivity after six years after the marketing authorisation has been abolished.

(103) In order to encourage faster and wider access also to orphan medicinal products, an additional period of one year of market exclusivity is granted to orphan medicinal products for a Union market launch, with the exception of well-established use medicinal products.

(104) To reward research into and development of new therapeutic indications, an additional period of one year of market exclusivity is provided for a new therapeutic indication (with a maximum of two indications).

(105) This Regulation includes several provisions aimed to avoid not-justified benefits being derived from the market exclusivity and to improve accessibility of medicinal products by ensuring faster entry of generics and biosimilars, and similar medicinal products on the market. It also clarifies the concurrence of market exclusivity with data protection and defines situations when a similar medicinal product may be granted a marketing authorisation, despite the ongoing market exclusivity.

(106) Before a medicinal product for human use is placed on the market in one or more Member States, it has to have undergone extensive studies, including non-clinical tests and clinical trials, to ensure that it is safe, of high quality and effective for use in the target population. It is important that such studies are undertaken also on the paediatric population in order to ensure that medicinal products are appropriately authorised for use in the paediatric population, and to improve the information available on the use of medicinal products in the various paediatric population. It is also important that medicinal products are presented in dosages and formulations adequate for the use in children.

(107) Therefore, the development of medicinal products that could potentially be used for the paediatric population should become an integral part of the development of medicinal products, integrated into the development programme for adults. Thus, paediatric investigation plans should be submitted early during medicinal product development, in time for studies to be conducted in the paediatric population, where appropriate, before marketing authorisation applications are submitted.

(108) As the development of medicinal products is a dynamic process dependent on the result of ongoing studies, in certain cases, for example when limited information on the medicinal products are available because the medicinal products are tested for the first time in the paediatric population, a specific procedure allowing to progressively build up a paediatric investigation plan should be put in place.

(109) During public health emergencies, in order not to delay a prompt authorisation of a medicinal product intended for the treatment or the prevention of a condition related to the public health emergency, there should be a possibility to temporarily waive the requirements concerning paediatric studies to be submitted at the moment of marketing authorisation.

(110) In order to not endanger the health of children and avoid to expose them to unnecessary clinical trials, the obligation to agree and conduct paediatric studies in children should be waived when the medicinal product is likely to be ineffective or unsafe in part or all of the paediatric population, the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for children or the disease for which the medicinal product is intended occurs only in adult populations. Nevertheless, in the last case, if on the basis of existing scientific evidence, the medicinal product due to its molecular mechanism of action is expected to be effective against a different disease in children, the obligation should be maintained.

(111) To ensure that research in the paediatric population is only conducted to meet their therapeutic needs, the Agency should agree and make public lists of waivers for medicinal products and for specific medicinal products or for classes or part of classes of medicinal products. As knowledge of science and medicine evolves over time, provision should be made for the lists of waivers to be amended. However, if a waiver is revoked, that requirement should not apply for a given period in order to allow time for at least a paediatric investigation plan to be agreed and studies in the paediatric population to be initiated before an application for marketing authorisation is submitted.

(112) With a view to ensuring that research is conducted only when safe and ethical and that the requirement for study data in the paediatric population does not block or delay the authorisation of medicinal products for other populations, the Agency may defer the initiation or completion of some or all of the measures contained in a paediatric investigation plan for a limited period of time. Such deferral should be extended only in duly justified cases.

(113) The possibility to modify an agreed paediatric investigation plan should be foreseen when the applicant encounters such difficulties with its implementation as to render the plan unworkable or no longer appropriate.

(114) The Agency, after consultation of the Commission and of interested parties, should draw up the details of the content of an application for agreement of a paediatric investigation plan, for its modification, for waivers and for deferral requests.

(115) For medicinal products intended to be developed for use only in children which would be developed independently from the current provisions, simplified details of the paediatric investigation plan should be required.

(116) To ensure that the data supporting the marketing authorisation concerning the use of a medicinal product in children to be authorised under this Regulation have been correctly developed, the Committee for Medicinal Products for Human Use should check compliance with the agreed paediatric investigation plan and any waivers and deferrals at the validation step for marketing authorisation applications.

(117) Free scientific advice should be provided by the Agency as an incentive to sponsors developing medicinal products for the paediatric population.

(118) To provide healthcare professionals and patients with information on the safe and effective use of medicinal products in the paediatric population, the results of the studies conducted in accordance with a paediatric investigation plan, independently from the fact that they support or not the use of the medicinal product in children, should be included in the summary of product characteristics and, if appropriate, in the package leaflet.

(119) To sustain the development of novel, paediatric only indications from authorised medicinal products no longer covered by intellectual property rights, it is necessary to establish a specific type of marketing authorisation, the Paediatric Use Marketing Authorisation. A Paediatric Use Marketing Authorisation should be granted through existing marketing authorisation procedures but should apply specifically for medicinal products developed exclusively for use in the paediatric population. It should be possible for the name of the medicinal product that has been granted a Paediatric Use Marketing Authorisation to retain the existing brand name of the corresponding medicinal product authorised for adults, in order to capitalise on existing brand recognition, while benefiting from the regulatory protection associated with a new marketing authorisation.

(120) An application for a Paediatric Use Marketing Authorisation should include the submission of data concerning use of the medicinal product in the paediatric population, collected in accordance with an agreed paediatric investigation plan. These data may be derived from the published literature or from new studies. An application for a Paediatric Use Marketing Authorisation should also be able to refer to data contained in the dossier of a medicinal product which is or has been authorised in the Union. This is intended to provide an additional incentive to encourage SMEs, including generic companies, to develop off-patent medicinal products for the paediatric population.

(121) Some paediatric investigation plans may be discontinued due to various reasons despite possible positive results for the treatment of children obtained from the studies already conducted. The information of such discontinuations and their reasons should be collected by the Agency and made public in order to inform eventual third parties who may be interested in continuing the above-mentioned studies.

(122) To increase the transparency on clinical trials conducted in children in third countries and referred to in a paediatric investigation plan or conducted from a marketing authorisation holder independently from a paediatric investigation plan, information on these clinical trials should be included in the European clinical trial database created by Regulation (EU) No 536/2014.

(123) The summary of the results of all the paediatric clinical trials included in the European clinical trial database created by Regulation (EU) No 536/2014 should be made publicly available within 6 months after the end of the clinical trials unless this is not possible for justified scientific reasons.

(124) To discuss priority in medicinal product development, in particular in areas of unmet medical need for children and to coordinate studies relating to paediatric medicinal products, the Agency should set up a European network composed of patient representatives, academics, medicines developers, investigators and research centres based in the Union or in the European Economic Area.

(125) Union funding should be provided to cover all aspects of the work of the Agency resulting from paediatric related activities, such as the assessment of paediatric

investigation plans, fee waivers for scientific advice, and information and transparency measures, including the database of paediatric studies and the network.

(126) It is necessary to take measures for the supervision of medicinal products authorised by the Union, and in particular for the intensive supervision of undesirable effects of these medicinal products within the framework of Union pharmacovigilance activities, so as to ensure the rapid withdrawal from the market of any medicinal product presenting a negative benefit-risk balance under normal conditions of use.

(127) The main tasks of the Agency in the area of pharmacovigilance laid down in Regulation (EC) No 726/2004 should be maintained. This includes the management of the Union pharmacovigilance database and data-processing network (the 'Eudravigilance database'), the coordination of safety announcements by the Member States and the provision to the public of information regarding safety issues. The Eudravigilance database should be the single point of receipt of pharmacovigilance information. Member States should therefore not impose any additional reporting requirements on marketing authorisation holders. The database should be fully and permanently accessible to the Member States, the Agency and the Commission, and accessible to an appropriate extent to marketing authorisation holders and the public.

(128) To enhance the efficiency of market surveillance, the Agency should be responsible for coordinating Member States' pharmacovigilance activities. A number of provisions are required to put in place stringent and efficient pharmacovigilance procedures, to allow the competent authority of the Member State to take provisional emergency measures, including the introduction of amendments to the marketing authorisation and, finally, to permit a reassessment to be made at any time of the risk-benefit balance of a medicinal product.

(129) Scientific and technological progresses in data analytics and data infrastructure are essential for the development, authorisation and supervision of medicinal products. The digital transformation has affected regulatory decision-making, making it more data-driven and multiplying the possibilities to access evidence, across the life cycle of a medicinal product. This Regulation recognises the Agency's experience and capacity to access and analyse data submitted independently from the marketing authorisation applicant or marketing authorisation holder. On this basis, the Agency should take initiative to update the summary of product characteristics in case new efficacy or safety data has an impact on the benefit-risk balance of a medicinal product.

(130) It is also appropriate to entrust the Commission, in close cooperation with the Agency and after consultations with the Member States, with the task of coordinating the execution of the various supervisory responsibilities vested in the Member States, and in particular with the tasks of providing information on medicinal products and of checking the observance of good manufacturing, laboratory and clinical practices.

(131) It is necessary to provide for the coordinated implementation of Union procedures for the marketing authorisation of medicinal products, and of the marketing authorisation procedures of Member States which have already been harmonised to a considerable degree by [revised Directive 2001/83/EC].

(132) The Union and Member States have developed a scientific evidence-based process that allows competent authorities to determine the relative effectiveness of new or existing medicinal products. This process focuses specifically on the added value of a medicinal product in comparison with other new or existing health technologies However, this evaluation should not be conducted in the context of the marketing

authorisation, for which it is agreed that the fundamental criteria should be retained. It is useful in this respect to allow for the possibility of gathering information on the methods used by the Member States to determine the therapeutic benefit obtained by each new medicinal product.

(133) Regulatory sandboxes can provide the opportunity for advancing regulation through proactive regulatory learning, enabling regulators to gain better regulatory knowledge and to find the best means to regulate innovations based on real-world evidence, especially at a very early stage of development of a medicinal product, which can be particularly important in the face of high uncertainty and disruptive challenges, as well as when preparing new policies. Regulatory sandboxes provide a structured context for experimentation, enable where appropriate in a real-world environment the testing of innovative technologies, products, services or approaches – at the moment especially in the context of digitalisation or the use of artificial intelligence and machine learning in the life cycle of medicinal products from drug discovery, development to the administration of medicinal products – for a limited time and in a limited part of a sector or area under regulatory supervision ensuring that appropriate safeguards are in place. In its conclusions of 23 December 2020 the Council has encouraged the Commission to consider the use of regulatory sandboxes on a case-by-case basis when drafting and reviewing legislation.

(134) In the area of medicinal products, a high level of protection of inter alia citizens, consumers, health, as well as legal certainty, a level playing field and fair competition always need to be ensured and existing levels of protection need to be respected.

(135) The establishment of a regulatory sandbox should be based on a Commission Decision following a recommendation of the Agency. Such decision should be based on a detailed plan outlining the particularities of the sandbox as well as describing the products to be covered. A regulatory sandbox should be limited in duration and may be terminated at any time based on public health considerations. The learning stemming from a regulatory sandbox should inform future changes to the legal framework to fully integrate the particular innovative aspects into the medicinal product regulation. Where appropriate, adapted frameworks may be developed by the Commission on the basis of the results of a regulatory sandbox.

(136) Shortages of medicinal products represent a growing threat to public health, with potential serious risks to the health of patients in the Union and impacts on the right of patients to access appropriate medical treatment. The root causes of shortages are multifactorial, with challenges identified along the entire pharmaceutical value chain, from quality and manufacturing problems. In particular, shortages of medicinal products can result from supply chain disruptions and vulnerabilities affecting the supply of key ingredients and components. Therefore, all marketing authorisation holders should have shortage prevention plans in place, to prevent shortages. The Agency should provide guidance to marketing authorisation holders on approaches to streamline the implementation of those plans.

(137) To achieve a better security of supply for medicinal products in the internal market and to contribute thereby to a high level of public health protection, it is appropriate to approximate the rules on monitoring and reporting of actual or potential shortages of medicinal products, including the procedures and the respective roles and obligations of concerned entities in this Regulation. It is important to ensure continued supply of medicinal products, which is often taken for granted across Europe. This is especially true for the most critical medicinal products which are essential to ensure the

continuity of care, the provision of quality healthcare and guarantee a high level of public health protection in Europe.

(138) The national competent authorities should be empowered to monitor shortages of medicinal products that are authorised through both national and centralised procedures, based on notifications of marketing authorisation holders. The Agency should be empowered to monitor shortages of medicinal products that are authorised through the centralised procedure, also based on notifications of marketing authorisation holders. When critical shortages are identified, both national competent authorities and the Agency should work in a coordinated manner to manage those critical shortages, whether the medicinal product concerned by the critical shortage is covered by a centralised marketing authorisation or a national marketing authorisation. Marketing authorisation holders and other relevant entities must provide the relevant information to inform the monitoring. Wholesale distributors and other persons or legal entities, including patient organisations or health care professionals, may also report a shortage of a given medicinal product marketed in the Member State concerned to the competent authority. The Executive Steering Group on Shortages and Safety of Medicinal Products ('the Medicines Shortages Steering Group' (MSSG)) already established within the Agency pursuant to Regulation (EU) 2022/123 of the European Parliament and of the Council[21], should adopt a list of critical shortages of medicinal products and ensure monitoring of those shortages by the Agency. The MSSG should also adopt a list of critical medicinal products authorised in accordance with [revised Directive 2001/83/EC] or this Regulation to ensure monitoring of the supply of those products. The MSSG may provide recommendations on measures to be taken by marketing authorisation holders, the Member States, the Commission and other entities to resolve any critical shortage or to ensure the security of supply of those critical medicinal products to the market. Implementing acts can be adopted by the Commission to ensure that appropriate measures, including the establishment or maintenance of contingency stocks, are taken by marketing authorisation holders, wholesale distributors or other relevant entities.

(139) To ensure continuity of supply and availability of critical medicinal products to the market, rules on the transfer of the marketing authorisation prior to the permanent marketing cessation should be laid down. Such transfer should not be considered to be a variation.

(140) It is recognised that improved access to information contributes to public awareness, gives the public the opportunity to express its observations and enables authorities to take due account of those observations. The general public should therefore have access to information in the Union Register of medicinal products, the Eudravigilance database and the manufacturing and wholesale distribution database, after the deletion of any commercially confidential information by the competent authority. Regulation (EC) No 1049/2001 of the European Parliament and of the Council[22] gives the fullest possible effect to the right of public access to documents and lays down the general principles and limits on such access. The Agency should therefore give the widest

[21] Regulation (EU) 2022/123 of the European Parliament and of the Council of 25 January 2022 on a reinforced role for the European Medicines Agency in crisis preparedness and management for medicinal products and medical devices (OJ L 20, 31.1.2022, p. 1).

[22] Regulation (EC) No 1049/2001 of the European Parliament and of the Council of 30 May 2001 regarding public access to European Parliament, Council and Commission documents (OJ L 145, 31.5.2001, p. 43).

possible access to the documents while carefully balancing the right for information with existing data protection requirements. Certain public and private interests, such as personal data and commercially confidential information, should be protected by way of exception in accordance with Regulation (EC) No 1049/2001.

(141) To ensure the enforcement of certain obligations relating to the marketing authorisation for medicinal products for human use granted in accordance with this Regulation, the Commission should be able to impose financial penalties. When assessing the responsibility for failures to comply with those obligations and imposing such penalties, it is important that means exist to address the fact that marketing authorisation holders could be part of a wider economic entity. Otherwise, there is a clear and identifiable risk that the responsibility for a failure to comply with those obligations could be evaded, which might have an impact on the ability to impose effective, proportional and dissuasive penalties. The penalties imposed should be effective, proportionate and dissuasive, having regard to the circumstances of the specific case. For the purposes of ensuring legal certainty in the conduct of the infringement procedure, it is necessary to set maximum amounts for penalties. Those maximum amounts should not be linked to the turnover of a particular medicinal product but the economic entity involved.

(142) To supplement or amend certain non-essential elements of this Regulation, the power to adopt acts in accordance with Article 290 of the Treaty on the Functioning of the European Union ('TFEU') should be delegated to the Commission in respect of determining the situations in which post-authorisation efficacy studies may be required; specifying the categories of medicinal products to which a marketing authorisation subject to specific obligations could be granted and specifying the procedures and requirements for granting such a marketing authorisation and for its renewal; specifying exemptions to variation and the categories in which variations should be classified and establishing procedures for the examination of applications for variations to the terms of marketing authorisations as well as specifying conditions and procedures for cooperation with third countries and international organisations for examination of applications for such variations; establishing procedures for the examination of applications for the transfer of marketing authorisations; laying down the procedure and rules for the imposition of fines or periodic penalty payments for a failure to comply with the obligations under this Regulation as well as the conditions and methods for their collection. The Commission should be empowered to adopt supplementary measures laying down the situations in which post-authorisation efficacy studies may be required. It is of particular importance that the Commission carries out appropriate consultations during its preparatory work, including at expert level, and that those consultations be conducted in accordance with the principles laid down in the Interinstitutional Agreement between the European Parliament, the Council of the European Union and the European Commission of 13 April 2016 on Better Law-Making[23]. In particular, to ensure equal participation in the preparation of delegated acts, the European Parliament and the Council receive all documents at the same time as Member States' experts, and their experts systematically have access to meetings of Commission expert groups dealing with the preparation of delegated acts.

(143) To ensure uniform conditions for the implementation of this Regulation in relation to marketing authorisations for medicinal products for human use, implementing powers

[23] OJ L 123, 12.5.2016, p. 1.

should be conferred on the Commission. The implementing powers related to the granting of centralised marketing authorisations and for suspending, revoking or withdrawing those authorisations, for granting vouchers, establishing and modifying regulatory sandboxes and decisions on the regulatory status of medicinal products should be exercised in accordance with Regulation (EU) 182/2011.

(144) Article 91 of Regulation (EU) No 536/2014 currently stipulates, amongst others, that it applies without prejudice to Directives 2001/18/EC and 2009/41/EC.

(145) Experience shows that, in clinical trials with investigational medicinal products containing or consisting of GMOs, the procedure to achieve compliance with the requirements of Directives 2001/18/EC and 2009/41/EC as regards the environmental risk assessment and consent by the competent authority of a Member State is complex and can take a significant amount of time.

(146) The complexity of that procedure increases greatly in the case of multi-centre clinical trials conducted in several Member States, as sponsors of clinical trials need to submit multiple requests for authorisation to multiple competent authorities in different Member States in parallel. In addition, national requirements and procedures for the environmental risk assessment (ERA) and written consent by competent authorities under GMO legislation vary greatly from one Member State to another as some Member States apply Directive 2001/18/EC, others apply Directive 2009/41/EC and there are Member States that apply either Directive 2009/41/EC or 2001/18/EC depending on the specific circumstances of a clinical trial. It is therefore not possible to determine a priori the national procedure that is to be followed.

(147) Consequently, it is particularly difficult to conduct multi-centre clinical trials with investigational medicinal products that contain or consist of GMOs involving several Member States.

(148) One of the objectives of Regulation (EU) No 536/2014 is that there will be a single coordinated and harmonised assessment of the clinical trial application between the involved Member States, with one country leading the coordination of the assessment (the Reporting Member State).

(149) It is therefore appropriate to envisage a centralised assessment of the ERA involving experts from the national competent authorities.

(150) Article 5 of Directive 2001/18/EC provides that the authorisation procedures for the deliberate release into the environment of GMOs and their related rules described in its Articles 6 to 11 do not apply for medicinal substances and compounds for human use if authorised by Union legal acts that fulfil the criteria listed in that Article.

(151) The requirement for the holding of authorisation of manufacturing and import of investigational medicinal products in the Union in accordance with Article 61(2), point (a), of Regulation (EU) No 536/2014 should be extended to investigational medicinal products containing or consisting of GMOs in Directive 2009/41/EC.

(152) It is thus judicious, in order to ensure an efficient functioning of Regulation (EU) No 536/2014, to define a specific authorisation procedure for the deliberate release of medicinal substances and compounds for human use containing or consisting of GMOs fulfilling the requirements of Article 5 of Directive 2001/18/EC and taking into account the specific characteristics of medicinal substances and compounds.

(153) Detailed rules concerning financial penalties for failure to comply with certain obligations laid down in this Regulation are specified in Commission Regulation (EC)

No 658/2007[24]. Those rules should be maintained, but it is appropriate to consolidate them by moving their core elements and the list specifying those obligations into this Regulation, while maintaining a delegation of powers that allows the Commission to supplement this Regulation by laying down procedures for imposing such financial penalties. It is appropriate, in order to provide for legal certainty, to clarify that Commission Regulation (EC) No 2141/96[25] remains in force and continues to apply unless and until repealed. For the same reason, it should be clarified that Regulations (EC) No 2049/2005[26], No 507/2006[27], No 658/2007 and (EC) No 1234/2008[28] remain in force and continue to apply unless and until repealed.

(154) This Regulation is based on the double legal basis of Article 114 and Article 168(4), point (c), TFEU. It aims at achieving an internal market as regards medicinal products for human use, taking as a base a high level of protection of health. At the same time, this Regulation sets high standards of quality and safety for medicinal products in order to meet common safety concerns as regards these products. Both objectives are being pursued simultaneously. These two objectives are inseparably linked and one is not secondary to another. Regarding Article 114 TFEU, this Regulation establishes a European Medicines Agency and provides specific provision with regard to the central authorisation of medicinal products, therefore ensuring the functioning of the internal market and the free movement of medicinal products. Regarding Article 168(4), point (c), TFEU, this Regulation sets high standards of quality and safety for medicinal products.

(155) This Regulation respects the fundamental rights and observes the principles recognised in particular by the Charter of Fundamental Rights of the European Union and notably human dignity, the integrity of the person, the rights of the child, respect for private and family life, the protection of personal data and the freedom of art and science.

(156) The objective of this Regulation is to ensure the authorisation of high quality medicinal products, including for paediatric patients and patients suffering from rare diseases throughout the Union. Where this objective cannot be sufficiently achieved by the Member States but can rather, by reason of its scale, be better achieved at Union level, the Union may adopt measures, in accordance with the principle of subsidiarity as set out in Article 5 of the Treaty on European Union. In accordance with the principle of proportionality, as set out in that Article, this Regulation does not go beyond what is necessary in order to achieve that objective.

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[24] Commission Regulation (EC) No 658/2007 of 14 June 2007 concerning financial penalties for infringement of certain obligations in connection with marketing authorisations granted under Regulation (EC) No 726/2004 of the European Parliament and of the Council (OJ L 155, 15.6.2007, p. 10).

[25] Commission Regulation (EC) No 2141/96 of 7 November 1996 concerning the examination of an application for the transfer of a marketing authorization for a medicinal product falling within the scope of Council Regulation (EC) No 2309/93 (OJ L 286, 8.11.1996, p. 6).

[26] Commission Regulation (EC) No 2049/2005 of 15 December 2005 laying down, pursuant to Regulation (EC) No 726/2004 of the European Parliament and of the Council, rules regarding the payment of fees to, and the receipt of administrative assistance from, the European Medicines Agency by micro, small and medium-sized enterprises (OJ L 329, 16.12.2005, p. 4).

[27] Commission Regulation (EC) No 507/2006 of 29 March 2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council (OJ L 92, 30.3.2006, p. 6).

[28] Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, p. 7).

HAVE ADOPTED THIS REGULATION:

CHAPTER I
SUBJECT MATTER, SCOPE AND DEFINITIONS

Article 1

Subject matter and scope

This Regulation lays down Union procedures for the authorisation, supervision and pharmacovigilance of medicinal products for human use at Union level, establishes rules and procedures at Union and at Member State level relating to the security of supply of medicinal products and lays down the governance provisions of the European Medicines Agency ('the Agency') established by Regulation (EC) No 726/2004 which shall carry out the tasks relating to medicinal products for human use that are laid down in this Regulation, Regulation (EU) No 2019/6 and other relevant Union legal acts.

This Regulation shall not affect the powers of Member States' authorities as regards setting the prices of medicinal products or their inclusion in the scope of the national health system or social security schemes on the basis of health, economic and social conditions. Member States may choose from the particulars shown in the marketing authorisation those therapeutic indications and pack sizes which will be covered by their social security bodies.

Article 2

Definitions

For the purposes of this Regulation, the definitions laid down in Article 4 of [revised Directive 2001/83/EC[29]] shall apply.

The following definitions shall also apply:

(1) 'veterinary medicinal product' means a medicinal product as defined in Article 4, point (1), of Regulation (EU) 2019/6;

(2) 'designated orphan medicinal product' means a medicinal product under development which has been granted an orphan designation by a decision referred to in Article 64(4);

(3) 'orphan medicinal products' means a medicinal product which has been granted an orphan marketing authorisation referred to in Article 69;

(4) 'orphan medicine sponsor' means any legal or natural person, established in the Union, who submitted an application for or has been granted an orphan designation by a decision referred to in Article 64(4);

(5) 'similar medicinal product' means a medicinal product containing a similar active substance or substances as contained in a currently authorised orphan medicinal product, and which is intended for the same therapeutic indication;

(6) 'similar active substance' means an identical active substance, or an active substance with the same principal molecular structural features (but not necessarily all of the same molecular structural features) and which acts via the same mechanism. In the case of advanced therapy medicinal products, for which the principal molecular

[29] [Name of revised Directive 2001/83/EC, date (OJ L XX, XX.XX.XXX, p. X).]

structural features cannot be fully defined, the similarity between two active substances shall be assessed on the basis of the biological and functional characteristics;

(7) 'significant benefit' means a clinically relevant advantage or a major contribution to patient care of an orphan medicinal product if such an advantage or contribution benefits a substantial part of the target population;

(8) 'clinically superior' means that a medicinal product is shown to provide a significant therapeutic or diagnostic advantage above that provided by an orphan medicinal product in one or more of the following ways:

(a) greater efficacy than an authorised medicinal orphan medicinal product in a substantial part of the target population;

(b) greater safety than an authorised medicinal product in a substantial part of the target population;

(c) in exceptional cases, where neither greater safety nor greater efficacy has been shown, demonstration that the medicinal product otherwise makes a major contribution to diagnosis or to patient care.

(11) 'paediatric use marketing authorisation' means a marketing authorisation granted in respect of a medicinal product for human use which is not protected by a supplementary protection certificate under Regulation (EC) No 469/2009 of the European Parliament and of the Council concerning the supplementary protection certificate for medicinal products[30] [OP please replace reference by new instrument when adopted], or by a patent which qualifies for the granting of the supplementary protection certificate, covering exclusively therapeutic indications which are relevant for use in the paediatric population, or subsets thereof, including the appropriate strength, pharmaceutical form or route of administration for that product.

(12) 'regulatory sandbox' means a regulatory framework during which it is possible to develop, validate and test in a controlled environment innovative or adapted regulatory solutions that facilitate the development and authorisation of innovative products which are likely to fall in the scope of this Regulation, pursuant to a specific plan and for a limited time under regulatory supervision.

(13) 'critical medicinal product' means a medicinal product for which insufficient supply results in serious harm or risk of serious harm to patients and identified using the methodology pursuant to Article 130(1), point (a).

(14) 'shortage' means a situation in which the supply of a medicinal product that is authorised and placed on the market in a Member State does not meet the demand for that medicinal product in that Member State.

(15) 'critical shortage in the Member State' means a shortage of a medicinal product, for which there is no appropriate alternative medicinal product available on the market in that Member State, and that shortage cannot be resolved.

[30] Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the supplementary protection certificate for medicinal products (OJ L 152, 16.6.2009, p. 1).

(16) ‘critical shortage’ means a critical shortage in the Member State for which coordinated Union level action is considered necessary to resolve that shortage in accordance with this Regulation.

Article 3

Centrally authorised medicinal products

1. A medicinal product listed in Annex I shall only be placed on the Union market if a marketing authorisation for that medicinal product has been granted by the Union in accordance with this Regulation (‘centralised marketing authorisation’).

2. Any medicinal product not listed in Annex I, may be granted a centralised marketing authorisation in accordance with this Regulation, if the product meets at least one of the following requirements:

   (a) the applicant shows that the medicinal product constitutes a significant therapeutic, scientific or technical innovation or that the granting of marketing authorisation in accordance with this Regulation is in the interest of patients' health at Union level, including as regards antimicrobial resistance and medicinal products for public health emergencies;

   (b) it is a medicinal product intended solely for paediatric use.

3. Homeopathic medicinal products shall not be granted a marketing authorisation in accordance with this Regulation.

4. The Commission shall grant and supervise centralised marketing authorisations for medicinal products for human use in accordance with Chapter II.

5. The Commission is empowered to adopt delegated acts in accordance with Article 175 to amend Annex I to adapt it to technical and scientific progress.

Article 4

Member State authorisation of generics of centrally authorised medicinal products

A generic medicinal product of a reference medicinal product authorised by the Union may be authorised by the competent authorities of the Member States in accordance with [revised Directive 2001/83/EC] under the following conditions:

(a) the application for marketing authorisation is submitted in accordance with Article 9 of [revised Directive 2001/83/EC];

(b) the summary of product characteristics and the package leaflet are in all relevant respects consistent with that of the medicinal product authorised by the Union.

Point (b), first subparagraph, shall not apply to those parts of summary of product characteristics and package leaflet referring to indications, posologies, pharmaceutical forms, methods or routes of administration or any other way in which the medicinal product may be used which were still covered by a patent or a supplementary protection certificate for medicinal products at the time when the generic medicinal product was marketed and where the applicant for the generic medicinal product has requested not to include this information in their marketing authorisation.

Chapter II
GENERAL PROVISIONS AND RULES ON APPLICATIONS

SECTION 1

APPLICATION FOR CENTRALISED MARKETING AUTHORISATIONS

Article 5

Submission of applications for marketing authorisations

1. The marketing authorisation holder for medicinal products covered by this Regulation shall be established in the Union. The marketing authorisation holder shall be responsible for the placing on the market of those medicinal products, whether done by that marketing authorisation holder or via one or more persons designated to that effect.

2. An applicant shall agree with the Agency the submission date of an application for a marketing authorisation.

3. An applicant shall submit an application for a marketing authorisation electronically to the Agency and in the formats made available by the Agency.

4. The applicant shall be responsible for the accuracy of the information and documentation submitted with respect to its application.

5. Within 20 days of receipt of an application, the Agency shall check whether all the information and documentation required in accordance with Article 6 have been submitted, that the application does not contain critical deficiencies that may prevent the evaluation of the medicinal product and decide whether the application is valid.

6. Where the Agency considers that the application is incomplete, or contains critical deficiencies that may prevent the evaluation of the medicinal product, it shall inform the applicant accordingly and set a time limit for submitting the missing information and documentation. That time limit may be extended once by the Agency.

   Upon receipt of the responses from the applicant to the request to submit the missing information and documentation, the Agency will determine whether the application can be considered valid. Where the Agency refuses to validate an application, it shall notify the applicant and state the reasons for such refusal.

   If the applicant fails to provide the missing information and documentation within the time limit, the application shall be considered to have been withdrawn.

7. The Agency shall draw up scientific guidelines for the identification of critical deficiencies that may prevent the evaluation of a medicinal product, in consultation with the European Commission and the Member States.

Article 6

Centralised marketing authorisation application

1. Each application for a centralised marketing authorisation of a medicinal product for human use shall specifically and completely include the particulars and documentation as referred to in Chapter II of [revised Directive 2001/83/EC]. In the

case of applications in accordance with Article 6(2), Article 10 and Article 12 of [revised Directive 2001/83/EC], this shall include the electronic submission of raw data, in accordance with Annex II of that Directive.

The documentation shall include a declaration to the effect that clinical trials carried out outside the Union meet the ethical requirements of Regulation (EU) No 536/2014. Those particulars and documentation shall take account of the unique, Union nature of the authorisation requested and, otherwise than in exceptional cases relating to the application of the law on trademarks pursuant to Regulation (EU) 2017/1001 of the European Parliament and of the Council[31], shall include the use of a single name for the medicinal product. The use of a single name does not exclude the use of additional qualifiers where necessary to identify different presentations of the medicinal product concerned.

2. For medicinal products that are likely to offer an exceptional therapeutic advancement in the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Union, the Agency may, following the advice of the Committee for Medicinal Products for Human Use regarding the maturity of the data related to the development, offer to the applicant a phased review of complete data packages for individual modules of particulars and documentation as referred to in paragraph 1.

   The Agency may at any stage suspend or cancel the phased review, where the Committee for Medicinal Products for Human Use considers that the submitted data are not of sufficient maturity or where it is considered that the medicinal product no longer fulfils an exceptional therapeutic advancement. The Agency shall inform the applicant accordingly.

3. A fee shall apply for a marketing authorisation application and shall be payable to the Agency for the examination of the application.

4. Where appropriate, the application may include an active substance master file certificate or an application for an active substance master file or any other quality master file certificate or application as referred to in Article 25 of [revised Directive 2001/83/EC].

5. The marketing authorisation applicant shall demonstrate that the principle of replacement, reduction and refinement of animal testing for scientific purposes has been applied in compliance with Directive 2010/63/EU with regard to any animal study conducted in support of the application.

   The marketing authorisation applicant shall not carry out animal tests in case scientifically satisfactory non-animal testing methods are available.

6. The Agency shall ensure that the opinion of the Committee for Medicinal Products for Human Use is given within 180 days after receipt of a valid application. In the case of a medicinal product for human use containing or consisting of genetically modified organisms, the opinion of that Committee shall take into account the evaluation of the environmental risk assessment in accordance with Article 8.

[31] Regulation (EU) 2017/1001 of the European Parliament and of the Council of 14 June 2017 on the European Union trade mark (OJ L 154, 16.6.2017, p. 1).

On the basis of a duly reasoned request, the Committee for Medicinal Products for Human Use may call for the duration of the analysis of the scientific data in the file concerning the application for marketing authorisation to be extended.

7. When an application is submitted for a marketing authorisation in respect of medicinal products for human use which are of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation, the applicant may request an accelerated assessment procedure. The same shall apply for products referred to in Article 60. The request shall be duly substantiated.

If the Committee for Medicinal Products for Human Use accepts the request, the time-limit laid down in Article 6(6), first subparagraph, shall be reduced to 150 days.

Article 7

Environmental risk assessment for medicinal products containing or consisting of genetically modified organisms

1. Without prejudice to Article 22 of [revised Directive 2001/83/EC], the marketing authorisation application of a medicinal product for human use containing or consisting of genetically modified organisms as defined in Article 2(2) of Directive 2001/18/EC shall be accompanied by an environmental risk assessment identifying and evaluating potential adverse effects of the genetically modified organisms on human health and the environment.

2. The environmental risk assessment for the medicinal products referred to in paragraph 1 shall be conducted in accordance with the elements described in Article 8 and the specific requirements set out in Annex II to [revised Directive 2001/83/EC] based on the principles set out in Annex II to Directive 2001/18/EC taking into account the specificities of medicinal products.

3. Articles 13 to 24 of Directive 2001/18/EC shall not apply to medicinal products for human use containing or consisting of genetically modified organisms.

4. Articles 6 to 11 of [revised Directive 2001/18/EC] as well as Articles 4 to 13 of Directive 2009/41/EC shall not apply to operations related to the supply and clinical use, including the packaging and labelling, distribution, storage, transport, preparation for administration, administration, destruction or disposal of medicinal products containing or consisting of genetically modified organisms, with the exception of their manufacture, in any of the following cases:

   (a) where such medicinal products have been excluded from the provisions of [revised Directive 2001/83/EC] by a Member State pursuant to Article 3(1) of that Directive;

   (b) where the use and distribution of such medicinal products have been temporarily authorised by a Member State pursuant to Article 3(2) of [revised Directive 2001/83/EC]; or

   (c) where such medicinal products are made available by a Member State pursuant to Article 26(1).

5. In the cases referred to in paragraph 4, Member States shall implement appropriate measures to minimise foreseeable negative environmental impacts resulting from the intended or unintended release of the medicinal products containing or consisting of genetically modified organisms into the environment.

The competent authorities of the Member States shall ensure that information related to the use of medicinal products referred to in paragraph 4, is available and provided to the competent authorities established by Directive 2009/41/EC, when necessary and in particular in the event of an accident referred to in Article 14 and Article 15 of Directive 2009/41/EC.

Article 8

Content of the environmental risk assessment for medicinal products containing or consisting of genetically modified organisms

The environmental risk assessment referred to in Article 7(2) shall contain the following elements:

(a) description of the genetically modified organism and the modifications introduced as well as characterisation of the finished product;

(b) identification and characterisation of hazards for the environment, animals and for human health;

(c) exposure characterisation, assessing the likelihood or probability that the identified hazards materialise;

(d) risk characterisation taking into account the magnitude of each possible hazard and the likelihood or probability of that adverse effect occurring;

(e) risk minimisation strategies proposed to address identified risks including specific containment measures to limit contact with the medicinal product.

Article 9

Procedure for the environmental risk assessment for medicinal products containing or consisting of genetically modified organisms

1. The applicant shall submit an environmental risk assessment referred to in Article 7(1) to the Agency.

   The Committee for Medicinal Products for Human Use shall assess the environmental risk assessment.

2. In case of first-in-class medicinal products or when a novel question is raised during the assessment of the submitted environmental risk assessment, the Committee for Medicinal Products for Human Use, or the rapporteur, shall carry out necessary consultations with bodies Member States have set up in accordance with Directive 2001/18/EC. They may also consult with relevant Union bodies. Details on the consultation procedure shall be published by the Agency at the latest by [OJ:12 months after the date of entry into force of this Regulation].

Article 10

Committee assessment of an application for marketing authorisation

1. When preparing its opinion, the Committee for Medicinal Products for Human Use shall verify that the particulars and documentation submitted in accordance with Article 6 comply with the requirements of [revised Directive 2001/83/EC], and shall examine whether the conditions specified in this Regulation for granting a marketing

authorisation are satisfied. When preparing its opinion, the Committee for Medicinal Products for Human Use may make the following requests:

(a) that an Official Medicines Control Laboratory or a laboratory that a Member State has designated for that purpose tests the medicinal product for human use, its starting materials, ingredients and, where necessary, its intermediate products or other constituents in order to ensure that the control methods employed by the manufacturer and described in the application documents are satisfactory;

(b) that the applicant supplements the particulars accompanying the application within a specific time period. In case of such a request, the time-limit set out in Article 6(6), first subparagraph, shall be suspended until the supplementary information requested is provided. Likewise, this time-limit shall be suspended for the time allowed for the applicant to prepare oral or written explanations.

2. Where within 90 days of the validation of the marketing authorisation application and during the assessment the Committee for Medicinal Products for Human Use considers that the submitted data are not of sufficient quality or maturity to complete the assessment, the assessment can be terminated. The Committee for Medicinal Products for Human Use shall summarise the deficiencies in writing. On this basis, the Agency shall inform the applicant accordingly and set a time limit to address the deficiencies. The application shall be suspended until the applicant addresses the deficiencies. If the applicant fails to address those deficiencies within the time limit set by the Agency, the application shall be considered as withdrawn.

Article 11

Certification of manufacturer

1. Upon receipt of a written request from the Committee for Medicinal Products for Human Use, a Member State shall forward the information demonstrating that the manufacturer of a medicinal product or the importer from a third country is able to manufacture the medicinal product concerned or carry out the necessary control tests, or both in accordance with the particulars and documents supplied by the applicant pursuant to Article 6.

2. The Committee for Medicinal Products for Human Use may, if it considers it necessary in order to complete the assessment, require the applicant to undergo a specific inspection of the manufacturing site of the medicinal product concerned.

The inspection shall be carried out within the time-limit set out in Article 6(6), first subparagraph, by inspectors from the Member State holding the appropriate qualifications. Those inspectors may be accompanied by a rapporteur or an expert appointed by the Committee, or by one or more inspectors of the Agency. The inspections may be carried out unannounced.

For manufacturing sites located in third countries, the inspection may be carried out by the Agency, following a request by the Member States and based on the procedure set out in Article 52.

Article 12

Committee Opinion

1. The Agency shall without undue delay inform the applicant if the opinion of the Committee for Medicinal Products for Human Use is that:

   (a) the application does not satisfy the criteria for marketing authorisation set out in this Regulation;

   (b) the application satisfies the criteria set out in this Regulation subject to changes required by the Agency to the summary of product characteristics are made;

   (c) the application satisfies the criteria set out in this Regulation provided that changes required by the Agency, to the labelling or package leaflet of the medicinal product, are made to ensure compliance with Chapter VI of [revised Directive 2001/83/EC];

   (d) where applicable, the application satisfies the criteria set out in Articles 18 and 19 subject to specific conditions therein.

2. Within 12 days of receipt of the opinion referred to in paragraph 1, the applicant may request by written notice to the Agency a re-examination of the opinion. In that case, the applicant shall provide the Agency with the detailed grounds for the request within 60 days after receipt of the opinion.

   The re-examination procedure may deal only with the points of the opinion initially identified by the applicant and may be based only on the scientific data available when the Committee for Medicinal Products for Human Use adopted the initial opinion.

   Within 60 days following receipt of the grounds for the request, the Committee for Medicinal Products for Human Use shall re-examine its opinion. The reasons for the conclusion reached shall be annexed to the final opinion.

3. Within 12 days after its adoption, the Agency shall send the final opinion of the Committee for Medicinal Products for Human Use to the Commission, to the Member States and to the applicant, together with a report describing the assessment of the medicinal product by the Committee for Medicinal Products for Human Use and stating the reasons for its conclusions.

4. If an opinion is favourable to the granting of the relevant marketing authorisation, the following documents shall be annexed to the opinion:

   (a) a summary of product characteristics referred to in Article 62 of [revised Directive 2001/83/EC] and corresponding to the assessment of the medicinal product;

   (b) a recommendation on the frequency of submission of periodic safety update reports;

   (c) details of any conditions or restrictions to be imposed on the supply or use of the medicinal product concerned, including the conditions under which the medicinal product may be made available to patients, in accordance with the criteria laid down in Chapter XII of [revised Directive 2001/83/EC];

   (d) details of any recommended conditions or restrictions with regard to the safe and effective use of the medicinal product;

   (e) details of any recommended measures for ensuring the safe use of the medicinal product to be included in the risk management system;

(f) where appropriate, details of any recommended obligation to conduct post-authorisation safety studies or to comply with obligations on the recording or reporting of suspected adverse reactions which are stricter than those referred to in Chapter VIII;

(g) where appropriate, details of any recommended obligation to conduct post-authorisation efficacy studies where concerns relating to some aspects of the efficacy of the medicinal product are identified and can be resolved only after the medicinal product has been marketed. Such an obligation to conduct such studies shall be based on the delegated acts adopted pursuant to Article 21 while taking into account the scientific guidance referred to in Article 123 of [revised Directive 2001/83/EC];

(h) where appropriate, details of any recommended obligation to conduct any other post-authorisation studies to improve the safe and effective use of the medicinal product;

(i) in case of medicinal products for which there is substantial uncertainty as to the surrogate endpoint relation to the expected health outcome, where appropriate and relevant for the benefit-risk balance, a post-authorisation obligation to substantiate the clinical benefit;

(j) where appropriate, details of any recommended obligation to conduct additional post-authorisation environmental risk assessment studies, collection of monitoring data or information on use, where concerns about risks to the environment or public health, including antimicrobial resistance need to be further investigated after the medicinal product has been marketed;

(k) the text of the labelling and package leaflet, presented in accordance with Chapter VI of [revised Directive 2001/83/EC];

(l) the assessment report as regards the results of the pharmaceutical and non-clinical tests and of the clinical trials, and as regards the risk management system and the pharmacovigilance system for the medicinal product concerned;

(m) where appropriate, to carry out medicinal product-specific validation studies to replace animal-based control methods with non-animal-based control methods.

5. When adopting its opinion, the Committee for Medicinal Products for Human Use shall include the criteria for the prescription or use of the medicinal products in accordance with Article 50(1) of [revised Directive 2001/83/EC].

SECTION 2

MARKETING AUTHORISATION DECISIONS

Article 13

Commission decision on the marketing authorisation

1. Within 12 days of receipt of the opinion of the Committee for Medicinal products for Human Use the Commission shall submit to the Standing Committee on Medicinal Products for Human Use referred to in Article 173(1) a draft of the decision on the application.

In duly justified cases, the Commission may return the opinion to the Agency for further consideration.

Where a draft decision envisages the granting of a marketing authorisation, it shall include or make reference to the documents referred to in Article 12(4).

Where a draft decision envisages the granting of a marketing authorisation subject to the conditions referred to in Article 12(4), points (c) to (j), it shall lay down deadlines for the fulfilment of the conditions, where necessary.

Where the draft decision differs from the opinion of the Agency, the Commission shall provide a detailed explanation of the reasons for the differences.

The Commission shall send the draft decision to the Member States and the applicant.

2. The Commission shall, by means of implementing acts, take a final decision within 12 days after obtaining the opinion of the Standing Committee on Medicinal Products for Human Use. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 173, paragraphs 2 and 3.

3. Where a Member State raises important new questions of a scientific or technical nature that have not been addressed in the opinion delivered by the Agency, the Commission may refer the application back to the Agency for further consideration. In that case, the procedures set out in paragraphs 1 and 2, shall start again upon reception of the reply of the Agency.

4. The Agency shall disseminate the documents referred to in Article 12(4), points (a) to (e), together with any deadlines laid down pursuant to paragraph 1, first subparagraph.

Article 14

Withdrawal of a marketing authorisation application

If an applicant withdraws an application for a marketing authorisation submitted to the Agency before an opinion has been given on the application, the applicant shall communicate its reasons for doing so to the Agency. The Agency shall make this information publicly available and shall publish the assessment report, if available, after deletion of all information of a commercially confidential nature.

Article 15

Refusal of a centralised marketing authorisation

1. The marketing authorisation shall be refused if, after verification of the particulars and documentation submitted in accordance with Article 6, the view is taken that:

   (a) the benefit-risk balance of the medicinal product is not favourable;

   (b) that the applicant has not properly or sufficiently demonstrated the quality, safety or efficacy of the medicinal product;

   (c) its qualitative and quantitative composition is not as declared;

   (d) the environmental risk assessment is incomplete or insufficiently substantiated by the applicant or if the risks identified in the environmental risk assessment have not been sufficiently addressed by the applicant;

(e) particulars or documentation provided by the applicant in accordance with Article 6, paragraphs 1 to 4, are incorrect;

(f) the labelling and package leaflet proposed by the applicant are not in accordance with Chapter VI of [revised Directive 2001/83/EC].

2. The refusal of a Union marketing authorisation shall constitute a prohibition on the placing on the market of the medicinal product concerned throughout the Union.

3. Information about all refusals and the reasons for them shall be made publicly available.

Article 16

Marketing authorisations

1. Without prejudice to Article 1, paragraphs 8 and 9 of [revised Directive 2001/83/EC], a marketing authorisation which has been granted in accordance with this Regulation shall be valid throughout the Union. It shall confer the same rights and obligations in each of the Member States as a marketing authorisation granted by that Member State in accordance with Article 5 of [revised Directive 2001/83/EC].

The Commission shall ensure that authorised medicinal products for human use are added to the Union Register of Medicinal Products and that they are given a number, which shall appear on the packaging.

2. Notification of marketing authorisation shall be published in the *Official Journal of the European Union*, quoting the date of marketing authorisation and the registration number in the Union Register of Medicinal Products, any International Non-proprietary Name (INN) of the active substance of the medicinal product, its pharmaceutical form, and any Anatomical Therapeutic Chemical Code (ATC).

3. The Agency shall immediately publish the assessment report on the medicinal product for human use and the reasons for its opinion in favour of granting marketing authorisation, after deletion of any information of a commercially confidential nature.

The European public assessment report (EPAR) shall include:

– a summary of the assessment report written in a manner that is understandable to the public. The summary shall contain in particular a section relating to the conditions of use of the medicinal product;

– a summary of environmental risk assessment studies and their results as submitted by the marketing authorisation holder and the assessment of the environmental risk assessment and the information referred to in Article 22(5) of [revised Directive 2001/83/EC] by the Agency.

4. After a marketing authorisation has been granted, the marketing authorisation holder shall inform the Agency of the dates of actual marketing of the medicinal product for human use in the Member States, taking into account the various presentations authorised.

The marketing authorisation holder shall notify the Agency and the competent authority of the Member State concerned of the following:

(a) its intention to permanently cease the marketing of a medicinal product in that Member State in accordance with Article 116(1), point (a); or

(b) its intention to temporarily suspend the marketing of a medicinal product in that Member State in accordance with Article 116(1), point (c); or

(c) a potential or actual shortage in that Member State in accordance with Article 116(1), point (d); and

its reasons for such action under points (a) and (b) in accordance with Article 24, as well as any other reason relating to precautionary actions with regard to quality, safety, efficacy and the environment.

Upon request by the Agency, particularly in the context of pharmacovigilance, the marketing authorisation holder shall provide the Agency with all data relating to the volume of sales of the medicinal product at Union level, broken down by Member State, and any data in the marketing authorisation holder's possession relating to the volume of prescriptions in the Union and its Member States.

Article 17

Validity and renewal of marketing authorisations

1. Without prejudice to paragraph 2, a marketing authorisation for a medicinal product shall be valid for an unlimited period.

2. By way of derogation from paragraph 1, the Commission may decide when granting an authorisation, on the basis of a scientific opinion by the Agency concerning the safety of the medicinal product, to limit the validity of the marketing authorisation to five years.

Where the validity of the marketing authorisation is limited to five years, the marketing authorisation holder shall apply to the Agency for a renewal of the marketing authorisation at least nine months before the marketing authorisation ceases to be valid.

Where a renewal application has been submitted in accordance with the second subparagraph, the marketing authorisation shall remain valid until a decision is adopted by the Commission in accordance with Article 13.

The marketing authorisation may be renewed on the basis of a re-evaluation by the Agency of the benefit-risk balance. Once renewed, the marketing authorisation shall be valid for an unlimited period.

Article 18

Marketing authorisation granted in exceptional circumstances

1. In exceptional circumstances where, in an application under Article 6 of [revised Directive 2001/83/EC] for a marketing authorisation of a medicinal product or a new therapeutic indication of an existing marketing authorisation under this Regulation, an applicant is unable to provide comprehensive data on the efficacy and safety of the medicinal product under normal conditions of use, the Commission may, by derogation to Article 6, grant an authorisation under Article 13, subject to specific conditions, where the following requirements are met:

(a) the applicant has demonstrated, in the application file, that there are objective and verifiable reasons not to be able to submit comprehensive data on the efficacy and safety of the medicinal product under normal conditions of use

based on one of the grounds set out in Annex II to [revised Directive 2001/83/EC];

(b) except for the data referred to in point (a), the application file is complete and satisfies all the requirements of this Regulation;

(c) specific conditions are included in the decision of the Commission, in particular to ensure the safety of the medicinal product as well to ensure that the marketing authorisation holder notifies to the competent authorities any incident relating to its use and takes appropriate action where necessary.

2. The maintenance of the authorised new therapeutic indication and the validity of the marketing authorisation granted in accordance with paragraph 1 shall be linked to the reassessment by the Agency of the conditions referred to in paragraph 1 after two years from the date when the new therapeutic indication was authorised or the marketing authorisation was granted, and thereafter at a risk-based frequency to be determined by the Agency and specified by the Commission in the marketing authorisation.

This reassessment shall be conducted on the basis of an application by the marketing authorisation holder to maintain the authorised new therapeutic indication or renew the marketing authorisation under exceptional circumstances.

Article 19

Conditional marketing authorisation

1. In duly justified cases, to meet an unmet medical need of patients, as referred to in Article 83(1), point (a), of [revised Directive 2001/83/EC], a conditional marketing authorisation or a new conditional therapeutic indication to an existing marketing authorisation authorised under this Regulation may be granted by the Commission to a medicinal product that is likely to address the unmet medical need in accordance with Article 83(1), point (b), of [revised Directive 2001/83/EC], prior to the submission of comprehensive clinical data provided that the benefit of the immediate availability on the market of that medicinal product outweighs the risk inherent in the fact that additional data are still required.

In emergency situations, a conditional marketing authorisation or a new conditional therapeutic indication referred to in the first subparagraph may be granted also where comprehensive non-clinical or pharmaceutical data have not been supplied.

2. Conditional marketing authorisations or a new conditional therapeutic indication referred to in paragraph 1 may be granted only if the benefit-risk balance of the medicinal product is favourable and the applicant is likely to be able to provide comprehensive data.

3. Conditional marketing authorisations or a new conditional therapeutic indication granted pursuant to this Article shall be subject to specific obligations. Those specific obligations and, where appropriate, the time limit for compliance shall be specified in the conditions to the marketing authorisation. Those specific obligations shall be reviewed annually by the Agency for the first three years after granting the authorisation and every two years thereafter.

4. As part of the specific obligations referred to in paragraph 3, the marketing authorisation holder of a conditional marketing authorisation granted pursuant to this

Article shall be required to complete ongoing studies, or to conduct new studies, with a view to confirming that the benefit-risk balance is favourable.

5. The summary of product characteristics and the package leaflet shall clearly mention that the conditional marketing authorisation for the medicinal product has been granted subject to specific obligations as referred to in paragraph 3.

6. By way of derogation from Article 17(1), an initial conditional marketing authorisation granted pursuant to this Article shall be valid for one year, on a renewable basis for the first three years after granting the authorisation and every two years thereafter.

7. When the specific obligations referred to in paragraph 3 have been fulfilled for a conditional marketing authorisation granted pursuant to this Article, the Commission may, following an application by the marketing authorisation holder, and after having received a favourable opinion from the Agency, grant a marketing authorisation pursuant to Article 13.

8. The Commission is empowered to adopt delegated acts in accordance with Article 175 to supplement this Regulation by establishing the following:

   (a) the categories of medicinal products to which paragraph 1 applies;

   (b) the procedures and requirements for granting a conditional marketing authorisation, for its renewal, and for adding a new conditional therapeutic indication to an existing marketing authorisation.

Article 20

Imposed post-authorisation studies

1. After the granting of a marketing authorisation, the Agency may consider that it is necessary that the marketing authorisation holder:

   (a) conducts a post-authorisation safety study if there are concerns about the risks of an authorised medicinal product. If the same concerns apply to more than one medicinal product, the Agency shall, following consultation with the Pharmacovigilance Risk Assessment Committee, encourage the marketing authorisation holders concerned to conduct a joint post-authorisation safety study;

   (b) conducts a post-authorisation efficacy study when the understanding of the disease or the clinical methodology indicate that previous efficacy evaluations might have to be revised significantly. The obligation to conduct the post-authorisation efficacy study shall be based on the delegated acts adopted pursuant to Article 21 while taking into account the scientific guidance referred to in Article 123 of [revised Directive 2001/83/EC];

   (c) conducts a post-authorisation environmental risk assessment study to further investigate the risks to the environment or public health due to the release of the medicinal product in the environment, if new concerns emerge on the authorised medicinal product, or other medicinal products containing the same active substance.

   If this obligation would apply to several medicinal products, the Agency shall encourage the marketing authorisation holders concerned to conduct a joint post authorisation environmental risk assessment study.

Where the Agency considers that any of the post-authorisations studies referred to in points (a) to (c) is necessary, it shall inform the marketing authorisation holder thereof in writing, stating the grounds for its assessment and shall include the objectives and timeframe for submission and conduct of the study.

2. The Agency shall provide the marketing authorisation holder with an opportunity to present written observations in response to its letter within a time limit which it shall specify, if the marketing authorisation holder so requests within 30 days of receipt of the letter.

3. On the basis of the written observations the Agency shall review its opinion.

4. Where the opinion of the Agency confirms the need for any of the post-authorisation studies referred to in paragraph 1, points (a) to (c), to be carried out, the Commission shall vary the marketing authorisation, by means of implementing acts, adopted pursuant to Article 13 to include the obligation as a condition of the marketing authorisation unless the Commission returns the opinion to the Agency for further consideration. For obligations under paragraph 1, points (a) and (b), the marketing authorisation holder shall update the risk management system accordingly.

Article 21

Post authorisation efficacy studies

The Commission is empowered to adopt delegated acts in accordance with Article 175, to supplement this Regulation by determining the situations in which post-authorisation efficacy studies may be required under Article 12(4), point (g), and Article 20(1), point (b).

Article 22

Risk management system

The marketing authorisation holder shall incorporate any condition of authorisation reflecting the elements referred to in Article 12(4), points (d) to (g), or in Article 20, or in Article 18(1) and Article 19 in their risk management system.

Article 23

Liability of the marketing authorisation holder

The granting of a marketing authorisation shall not affect the civil or criminal liability of the manufacturer or of the marketing authorisation holder pursuant to the applicable national law in Member States.

Article 24

Suspension of marketing, withdrawal from the market of a medicinal product, withdrawal of a marketing authorisation by the marketing authorisation holder

1. In addition to the notification made pursuant to Article 116, the marketing authorisation holder shall notify the Agency without undue delay of any action they take to suspend the marketing of a medicinal product, to withdraw a medicinal product from the market, to request the withdrawal of a marketing authorisation or not to apply for the renewal of a marketing authorisation, together with the reasons for such action.

The marketing authorisation holder shall declare if such action is based on the following grounds:

(a) the medicinal product is harmful;

(b) it lacks therapeutic efficacy;

(c) the benefit-risk balance is not favourable;

(d) its qualitative and quantitative composition is not as declared;

(e) the controls on the medicinal product or on the ingredients and the controls at an intermediate stage of the manufacturing process have not been carried out or if some other requirement or obligation relating to the grant of the manufacturing authorisation has not been fulfilled; or

(f) a serious risk to the environment or to public health via the environment has been identified and not sufficiently addressed by the marketing authorisation holder.

Where the action referred to in the first subparagraph is to withdraw a medicinal product from the market, the marketing authorisation holder shall provide information on the impact of such withdrawal on patients who are already being treated.

The notification of the permanent withdrawal of a medicinal product from the market or of the temporary suspension of the marketing authorisation, or of the permanent withdrawal of a marketing authorisation or of the temporary disruption in supply of a medicinal product shall be made in accordance with Article 116(1).

2. The marketing authorisation holder shall make the notification pursuant to paragraph 1 if the action is taken in a third country and such action is based on any of the grounds set out in Articles 195 or 196(1) of [revised Directive 2001/83/EC].

3. In the cases referred to in paragraphs 1 and 2, the Agency shall forward the information to the competent authorities of the Member States without undue delay.

4. Where the marketing authorisation holder intends to permanently withdraw the marketing authorisation for a critical medicinal product, the marketing authorisation holder shall, prior to the notification referred to in paragraph 1, offer, on reasonable terms, to transfer the marketing authorisation to a third party that has declared its intention to place that critical medicinal product on the market, or to use the pharmaceutical non-clinical and clinical documentation contained in the file of the medicinal product for the purposes of submitting an application in accordance with Article 14 of [revised Directive 2001/83/EC].

Article 25

Duplicate marketing authorisations

1. Only one marketing authorisation may be granted to an applicant for a specific medicinal product.

By way of derogation from the first subparagraph, the Commission shall authorise the same applicant to submit more than one application to the Agency for that medicinal product in either of the following cases:

(a) if one of its indications or pharmaceutical forms is protected by a patent or a supplementary protection certificate in one or more Member States;

(b) for reasons of co-marketing with a different undertaking not belonging to the same group as the marketing authorisation holder of the medicinal product for which a duplicate is requested.

As soon as the relevant patent or supplementary protection certificate referred to in point (a) expires, the marketing authorisation holder shall withdraw the initial or duplicate marketing authorisation.

2. As regards medicinal products for human use, Article 187(3) of [revised Directive 2001/83/EC] shall apply to medicinal products authorised under this Regulation.

3. Without prejudice to the unique Union nature of the content of the documents referred to in Article 12(4), points (a) to (k), this Regulation shall not prohibit the use of two or more commercial designs for a given medicinal product for human use covered by a single marketing authorisation.

Article 26

Medicinal products for compassionate use

1. By way of derogation from Article 5 of [revised Directive 2001/83/EC] Member States may make available for compassionate use a medicinal product for human use belonging to the categories referred to in Article 3, paragraphs 1 and 2. This may include new therapeutic uses of an authorised medicinal product.

2. For the purposes of this Article, 'compassionate use' shall mean making a medicinal product belonging to the categories referred to in Article 3, paragraphs 1 and 2 available for compassionate reasons to a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who cannot be treated satisfactorily by an authorised medicinal product. The medicinal product concerned must either be the subject of an application for a marketing authorisation in accordance with Article 6 or the submission of such application is imminent, or it must be undergoing clinical trials in the same indication.

3. When applying paragraph 1, the Member State shall notify the Agency.

4. When compassionate use is envisaged by a Member State, the Committee for Medicinal Products for Human Use, after consulting the manufacturer or the applicant, may adopt opinions on the conditions for use, the conditions for distribution and the patients targeted. The opinions shall be updated where necessary.

In the preparation of the opinion, the Committee for Medicinal Products for Human Use may request information and data from marketing authorisation holders and from developers and may engage with them in preliminary discussions. The Committee may also make use of health data generated outside of clinical studies, where available, taking into account the reliability of those data.

The Agency may also liaise with the third country agencies for medicinal products with respect to additional information and data exchanges.

In the preparation of its opinion, the Committee for Medicinal Products for Human Use may consult the Member State concerned and request it to provide any available information or data that the Member State has in its possession relating to the medicinal product concerned.

5. Member States shall take account of any available opinion and notify the Agency of the making available of products on the basis of the opinion in their territory. Member States shall ensure that pharmacovigilance requirements are applied for those products. Article 106, paragraphs 1 and 2, as regards the recording and reporting of suspected adverse reactions and the submission of periodic safety update reports respectively, shall apply *mutatis mutandis*.

6. The Agency shall keep an up-to-date list of the opinions adopted in accordance with paragraph 4 and shall publish it on its website.

7. The opinions referred to in paragraph 4 shall not affect the civil or criminal liability of the manufacturer or of the applicant for marketing authorisation.

8. Where a compassionate use programme has been set up in accordance with paragraphs 1 and 5, the applicant shall ensure that patients taking part also have access to the new medicinal product during the period between authorisation and placing on the market.

9. This Article shall be without prejudice to Regulation (EU) No 536/2014 and to Article 3 of [revised Directive 2001/83/EC].

10. The Agency may adopt detailed guidelines laying down format and content of notifications referred to in paragraphs 3 and 5, and data exchange under this Article.

Article 27

Request for opinion on scientific matters

At the request of the Executive Director of the Agency or the Commission, the Committee for Medicinal Products for Human Use shall draw up an opinion on any scientific matter concerning the evaluation of medicinal products for human use. That Committee shall take due account of any requests by Member States for an opinion.

The Agency shall publish the opinion after deletion of any information of a commercially confidential nature.

Article 28

Regulatory decisions on marketing authorisations

An authorisation to place a medicinal product covered by this Regulation on the market shall not be granted, refused, varied, suspended, withdrawn or revoked except through the procedures and on the grounds set out in this Regulation.

Article 29

Regulatory protection periods

Without prejudice to the law on the protection of industrial and commercial property, medicinal products for human use which have been authorised in accordance with this Regulation shall benefit from the periods of regulatory protection set out in Chapter VII of [revised Directive 2001/83/EC].

SECTION 3

TEMPORARY EMERGENCY MARKETING AUTHORISATION

Article 30

Temporary emergency marketing authorisation

During a public health emergency, the Commission may grant a temporary emergency marketing authorisation ('TEMA') for medicinal products intended for the treatment, prevention or medical diagnosis of a serious or life-threatening disease or condition which are directly related to the public health emergency, prior to the submission of the complete quality, non-clinical, clinical data and environmental data and information.

Where medicinal products containing or consisting of genetically modified organisms in the sense of Article 2(2) of Directive 2001/18/EC are concerned, Articles 13 to 24 of that Directive shall not apply.

An application for a temporary emergency marketing authorisation shall be submitted in accordance with Articles 5 and 6.

Article 31

Criteria for granting a temporary emergency marketing authorisation

A temporary emergency marketing authorisation may be granted only after the recognition of a public health emergency at Union level in accordance with Article 23 of Regulation (EU) 2022/2371 of the European Parliament and of the Council[32] and where the following requirements are met:

(a) there is no other satisfactory method of treatment, prevention or diagnosis authorised or sufficiently available in the Union or, if such method is already available, the temporary emergency marketing authorisation of the medicinal product will contribute to address the public health emergency;

(b) based on the scientific evidence available, the Agency issues an opinion concluding that the medicinal product could be effective in treating, preventing or diagnosing the disease or condition directly related to the public health emergency, and the known and potential benefits of the product outweigh the known and potential risks of the product, taking into consideration the threat posed by the public health emergency.

Article 32

Scientific opinion

1. The Agency shall ensure that the scientific opinion of the Committee for Medicinal Products for Human Use is given without undue delay, taking into account, the recommendation of the Emergency Task Force referred to in Article 38(1), second subparagraph. For the purpose of issuing its opinion, the Agency may consider any relevant data on the medicinal product concerned.

[32] Regulation (EU) 2022/2371 of the European Parliament and of the Council of 23 November 2022 on serious cross-border threats to health and repealing Decision No 1082/2013/EU (OJ L 314, 6.12.2022, p. 26).

2. The Agency shall review any new evidence provided by the developer, the Member States or the Commission, or any other evidence that comes to its attention, in particular evidence that might influence the benefit-risk balance of the medicinal product concerned.

The Agency shall update its scientific opinion as necessary.

3. The Agency shall transmit without undue delay to the Commission the scientific opinion and its updates and any recommendations on the temporary emergency marketing authorisation.

Article 33

Commission decision for a temporary emergency marketing authorisation

1. On the basis of the scientific opinion of the Agency or its updates referred to in Article 32, paragraphs 1 and 2, the Commission shall, by means of implementing acts, take a decision without undue delay on the temporary emergency marketing authorisation of the medicinal product subject to the specific conditions set in accordance with paragraphs 2, 3 and 4. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 173(2).

2. On the basis of the scientific opinion of the Agency referred to in paragraph 1, the Commission shall set specific conditions with respect to the temporary emergency marketing authorisation, in particular the conditions for manufacturing, use, supply and safety monitoring and the compliance with related good manufacturing, and pharmacovigilance practices. If necessary, the conditions may specify the batches of the medicinal product concerned by the temporary emergency marketing authorisation.

3. Specific conditions may be set to require the completion of ongoing studies or to conduct new studies to ensure the safe and effective use of the medicinal product or minimise its impact on the environment. A time limit for the submission of those studies shall be set.

4. Those specific conditions and, where appropriate, the time limit for compliance shall be specified in the conditions to the marketing authorisation and shall be reviewed annually by the Agency.

Article 34

Validity of a temporary emergency marketing authorisation

The temporary emergency marketing authorisation shall cease to be valid when the Commission terminates the recognition of a public health emergency in accordance with Article 23(2) and (4) of Regulation (EU) 2022/2371.

Article 35

Variation, suspension or revocation of a temporary emergency marketing authorisation

The Commission may suspend, revoke or vary the temporary emergency marketing authorisation by means of implementing acts at any time in any of the following cases:

(a) the criteria laid down in Article 31 are no longer met;

(b) it is appropriate to protect public health;

(c) the marketing authorisation holder of a temporary emergency marketing authorisation has not complied with conditions and obligations set out in the temporary emergency marketing authorisation;

(d) the marketing authorisation holder of a temporary emergency marketing authorisation has not complied with the specific conditions set in accordance with Article 33.

Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 173(2).

Article 36

Granting of a marketing authorisation or conditional marketing authorisation after a temporary emergency marketing authorisation

The marketing authorisation holder of an authorisation in accordance with Article 33 may submit an application in accordance with Articles 5 and 6 in order to obtain an authorisation in accordance with Articles 13, 16 or 19.

For the purpose of regulatory data protection, the temporary emergency marketing authorisation and any subsequent marketing authorisation, as referred to in subparagraph 1, shall be considered as part of the same global marketing authorisation.

Article 37

Transitional period

When the temporary marketing authorisation of a medicinal product is suspended or revoked for reasons other than the safety of the medicinal product, or if that temporary emergency marketing authorisation ceases to be valid, Member States may, in exceptional circumstances, allow for a transitional period, the supply of the medicinal product to patients who are already being treated with it.

Article 38

Relation with Article 18 of Regulation (EU) 2022/123

1. For medicinal products for which a temporary emergency marketing authorisation may be considered by the Agency, Article 18(1) and (2) of Regulation (EU) 2022/123[33] shall apply.

   The Emergency Task Force shall provide a recommendation for a temporary emergency marketing authorisation to the Committee for Medicinal Products for Human Use for an opinion in accordance with Article 32. To this purpose, the Emergency Task Force set up pursuant to Article 15 of Regulation (EU) 2022/123 may, where appropriate, perform the activities referred to in Article 18(2) of that Regulation prior to the recognition of a public health emergency.

2. Where a request referred to in Article 18(3) of Regulation (EU) 2022/123 for a recommendation has been made and there is an application for a temporary

[33] Regulation (EU) 2022/123 of the European Parliament and of the Council of 25 January 2022 on a reinforced role for the European Medicines Agency in crisis preparedness and management for medicinal products and medical devices (OJ L 20, 31.1.2022, p. 1).

emergency marketing authorisation for the medicinal product concerned, the procedure for a recommendation under Article 18(3) of Regulation (EU) 2022/123 shall be stopped and the procedure for a temporary emergency marketing authorisation shall prevail. Any available data shall be considered under the temporary emergency marketing authorisation application.

Article 39

Withdrawal of authorisations granted in accordance with Article 3(2) of [revised Directive 2001/83/EC]

When the Commission has granted a temporary emergency marketing authorisation in accordance with Article 33, Member States shall withdraw any authorisation granted in accordance with Article 3(2) of [revised Directive 2001/83/EC] for the use of medicinal products containing the same active substance for any indications that are subject to the temporary marketing authorisation.

CHAPTER III
INCENTIVES FOR THE DEVELOPMENT OF 'PRIORITY ANTIMICROBIALS'

Article 40

Granting the right to a transferable data exclusivity voucher

1. Following a request by the applicant when applying for a marketing authorisation, the Commission may, by means of implementing acts, grant a transferable data exclusivity voucher to a 'priority antimicrobial' referred to in paragraph 3, under the conditions referred to in paragraph 4 based on a scientific assessment by the Agency.

2. The voucher referred to in paragraph 1 shall give the right to its holder to an additional 12 months of data protection for one authorised medicinal product.

3. An antimicrobial shall be considered 'priority antimicrobial' if preclinical and clinical data underpin a significant clinical benefit with respect to antimicrobial resistance and it has at least one of the following characteristics:

   (a) it represents a new class of antimicrobials;

   (b) its mechanism of action is distinctly different from that of any authorised antimicrobial in the Union;

   (c) it contains an active substance not previously authorised in a medicinal product in the Union that addresses a multi-drug resistant organism and serious or life threatening infection.

   In the scientific assessment of the criteria referred to in the first subparagraph, and in the case of antibiotics, the Agency shall take into account the 'WHO priority pathogens list for R&D of new antibiotics', or an equivalent list established at Union level.

4. To be granted the voucher by the Commission, the applicant shall:

   (a) demonstrate capacity to supply the priority antimicrobial in sufficient quantities for the expected needs of the Union market;

(b) provide information on all direct financial support received for research related to the development of the priority antimicrobial.

Within 30 days after the marketing authorisation is granted, the marketing authorisation holder shall make the information referred to in point (b) accessible to the public via a dedicated webpage and shall communicate, in a timely manner the electronic link to that webpage to the Agency.

Article 41

Transfer and use of the voucher

1. A voucher may be used to extend the data protection for a period of 12 months of the priority antimicrobial or another medicinal product authorised in accordance with this Regulation of the same or different marketing authorisation holder.

   A voucher shall only be used once and in relation to a single centrally authorised medicinal product and only if that product is within its first four years of regulatory data protection.

   A voucher may only be used if the marketing authorisation of the priority antimicrobial for which the right was initially granted has not been withdrawn.

2. To use the voucher, its owner shall apply for a variation of the marketing authorisation concerned in accordance with Article 47 to extend the data protection.

3. A voucher may be transferred to another marketing authorisation holder and shall not be transferred further.

4. A marketing authorisation holder to whom a voucher is transferred shall notify the Agency of the transfer within 30 days, stating the value of the transaction between the two parties. The Agency shall make this information publicly available.

Article 42

Validity of the voucher

1. A voucher shall cease to be valid in the following cases:

   (a) where the Commission adopts a decision in accordance with Article 47 to extend the data protection of the receiving medicinal product;

   (b) where it is not used within 5 years from the date it was granted.

2. The Commission may revoke the voucher prior to its transfer as referred to in Article 41(3) if a request for supply, procurement or purchase of the priority antimicrobial in the Union has not been fulfilled.

3. Without prejudice to patent rights, or supplementary protection certificates[34], if a priority antimicrobial is withdrawn from the Union market prior to expiry of the periods of market and data protection laid down in Articles 80 and 81 of [revised Directive 2001/83/EC], those periods shall not prevent the validation, authorisation and placing on the market of a medicinal product using the priority antimicrobial as a

[34] Regulation (EC) No 469/2009 of the European Parliament and of the Council, (OJ L 152, 16.6.2009, p. 1).

reference medicinal product in accordance with Chapter II, Section 2 of [revised Directive 2001/83].

Article 43

Duration of application of Chapter III

This Chapter shall apply until [*Note to OP: insert the date of 15 years after the date of entry into force of this Regulation*] or until the date when the Commission has granted a total of 10 vouchers in accordance with this Chapter, whichever date is the earliest.

CHAPTER IV
POST-MARKETING AUTHORISATION MEASURES

Article 44

Urgent safety or efficacy restrictions

1. If, in the event of a risk to public health, the marketing authorisation holder takes urgent safety or efficacy restrictions on their own initiative, the marketing authorisation holder shall immediately inform the Agency.

   If the Agency has not raised objections within 24 hours following receipt of the information, the urgent safety or efficacy restrictions shall be deemed temporarily accepted.

   The marketing authorisation holder shall submit the corresponding application for variation within 15 days following initiation of that restriction in accordance with Article 47.

2. In the event of a risk to public health, the Commission may vary the marketing authorisation to impose urgent safety or efficacy restrictions on the marketing authorisation holder.

   The Commission shall take the decision to amend the marketing authorisation by means of implementing acts.

   Where the Commission decision in accordance with this Article imposes restrictions with regard to the safe and effective use of the medicinal product, it may also adopt a decision addressed to the Member States pursuant to Article 57.

   Where the marketing authorisation holder disagrees with the Commission decision, they may provide to the Agency written observations on the variation within 15 days of their receipt of the Commission decision. The Agency shall, based on the written observation, issue an opinion whether an amendment of the variation is required.

   If an amendment of the variation is required, the Commission shall take a final decision in accordance with the examination procedure referred to in Article 173(2).

   If a referral under Article 55 of this Regulation or under Article 95 or 114 of [revised Directive 2001/83/EC] is launched on the same safety or efficacy concern covered by this variation, any written observation provided by the marketing authorisation holder shall be considered in that referral.

Article 45

Update of a marketing authorisation related to scientific and technological developments

1. After a marketing authorisation has been granted in accordance with this Regulation, the marketing authorisation holder shall, in respect of the methods of manufacture and control provided for in Annex I, points (6) and (10), to [revised Directive 2001/83/EC], take account of scientific and technical progress and introduce any changes that may be required to enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods. The marketing authorisation holder shall apply for approval of corresponding variations in accordance with Article 47 of this Regulation.

2. The marketing authorisation holder shall without undue delay provide the Agency, the Commission and the Member States with any new information which might entail the amendment of the particulars or documentation referred to in Annex I, Articles 11, 28, 41 or 62 of [revised Directive 2001/83/EC], in Annex II to that Directive, or in Article 12(4) of this Regulation.

   The marketing authorisation holder shall without undue delay inform the Agency and the Commission of any prohibition or restriction imposed on the marketing authorisation holder or any entity in contractual relationship with the marketing authorisation holder by the competent authorities of any country in which the medicinal product is marketed and of any other new information which might influence the evaluation of the benefits and risks of the medicinal product concerned. The information shall include both positive and negative results of clinical trials or other studies in all indications and populations, whether or not included in the marketing authorisation, as well as data on the use of the medicinal product where such use is outside the terms of the marketing authorisation.

3. The marketing authorisation holder shall ensure that the product information and the terms of the marketing authorisation including the summary of product characteristics, the labelling and package leaflet are kept up to date with the current scientific knowledge including the conclusions of the assessment and recommendations made public by means of the European medicines web-portal set-up in accordance with Article 104.

4. The Agency may at any time request the marketing authorisation holder to submit data demonstrating that the benefit-risk balance remains favourable. The marketing authorisation holder shall answer fully and promptly any such request. The marketing authorisation holder shall also respond fully and within the time limit set to any request of a competent authority regarding the implementation of any measures previously imposed, including risk minimisation measures.

   The Agency may at any time ask the marketing authorisation holder to submit a copy of the pharmacovigilance system master file. The marketing authorisation holder shall submit that copy at the latest seven days after receipt of the request.

   The marketing authorisation holder shall also respond fully and within the time limit set to any request of a competent authority regarding the implementation of any measures previously imposed with regard to risks to the environment or public health, including antimicrobial resistance.

Article 46

Update of risk management plans

1. The marketing authorisation holder of a medicinal product referred to in Articles 9, and 11 of [revised Directive 2001/83/EC] shall submit to the Agency a risk

management plan and a summary thereof, where the marketing authorisation for the reference medicinal product is withdrawn but the marketing authorisation for the medicinal product referred to in Articles 9 and 11 of [revised Directive 2001/83/EC] is maintained.

The risk management plan and the summary thereof shall be submitted to the Agency within 60 days of the withdrawal of the marketing authorisation for the reference medicinal product by means of a variation in accordance with Article 47.

2. The Agency may impose an obligation on a marketing authorisation holder for a medicinal product referred to in Articles 9, 10, 11 and 12 of [revised Directive 2001/83/EC] to submit a risk management plan and summary thereof where:

(a) additional risk minimisation measures have been imposed concerning the reference medicinal product; or

(b) it is justified on pharmacovigilance grounds.

3. In the case mentioned referred to in paragraph 2, point (a), the risk management plan shall be aligned with the risk management plan for the reference medicinal product.

4. The imposition of the obligation referred to in paragraph 3, shall be duly justified in writing, notified to the marketing authorisation holder and shall include the deadline for submission of the risk management plan and the summary by means of a variation in accordance with Article 47.

Article 47

Variation of marketing authorisation

1. An application for variation of a centralised marketing authorisation by the marketing authorisation holder shall be made electronically in the formats made available by the Agency, unless the variation is an update by the marketing authorisation holder of their information held in a database.

2. Variations shall be classified in different categories depending on the level of risk to public health and the potential impact on the quality, safety and efficacy of the medicinal product concerned. Those categories shall range from changes to the terms of the marketing authorisation that have the highest potential impact on the quality, safety or efficacy of the medicinal product, to changes that have no or minimal impact thereon and to administrative changes.

3. The procedures for examination of applications for variations shall be proportionate to the risk and impact involved. Those procedures shall range from procedures that allow implementation only after approval based on a complete scientific assessment to procedures that allow immediate implementation and subsequent notification by the marketing authorisation holder to the Agency. Such procedures may also include updates by the marketing authorisation holder of their information held in a database.

4. The Commission is empowered to adopt delegated acts in accordance with Article 175 to supplement this Regulation by establishing the following:

(a) the categories referred to in paragraph 2 in which variations shall be classified;

(b) procedures for the examination of applications for variations to the terms of marketing authorisations, including procedures for updates through a database;

(c) the conditions for submission of a single application for more than one change to the terms of the same marketing authorisation and for the same change to the terms of several marketing authorisations;

(d) specifying exemptions to the variation procedures where the update of information in the marketing authorisation referred to in Annex I may be directly implemented;

(e) the conditions and procedures for cooperation with competent authorities of third countries or international organisations on examination of applications for variations to the terms of marketing authorisation.

Article 48

Scientific opinion on data submitted from not-for-profit entities for repurposing of authorised medicinal products

1. An entity not engaged in an economic activity ('not-for-profit entity') may submit to the Agency or to a competent authority of the Member State substantive non-clinical or clinical evidence for a new therapeutic indication that is expected to fulfil an unmet medical need.

   The Agency may, at the request of a Member State, the Commission, or on its own initiative and on the basis of all available evidence make a scientific evaluation of the benefit-risk of the use of a medicinal product with a new therapeutic indication that concerns an unmet medical need.

   The opinion of the Agency shall be made publicly available and the competent authorities of the Member States shall be informed.

2. In cases where the opinion is favourable, marketing authorisation holders of the medicinal products concerned shall submit a variation to update the product information with the new therapeutic indication.

3. Article 81(2), point (c) of [revised Directive 2001/83/EC] shall not apply for variations under this Article.

Article 49

Transfer of marketing authorisation

1. A marketing authorisation may be transferred to a new marketing authorisation holder. Such a transfer shall not be considered to be a variation. The transfer shall be subject to prior approval by the Commission, by means of implementing acts, following the submission of an application for the transfer to the Agency.

2. The Commission is empowered to adopt delegated acts in accordance with Article 175 to supplement this Regulation by establishing procedures for the examination of applications to the Agency for the transfer of marketing authorisations.

Article 50

Supervisory authority

1. In the case of medicinal products manufactured within the Union, the supervisory authorities for manufacturing shall be the competent authorities of the Member State or Member States which granted the manufacturing authorisation referred to in

Article 142(1) of [revised Directive 2001/83/EC] in respect of the medicinal product concerned.

2. In the case of medicinal products imported from third countries, the supervisory authorities for imports shall be the competent authorities of the Member State or Member States that granted the authorisation referred to in Article 142(3) of [revised Directive 2001/83/EC] to the importer, unless appropriate agreements have been made between the Union and the exporting country to ensure that those controls are carried out in the exporting country and that the manufacturer applies standards of good manufacturing practice at least equivalent to those laid down by the Union.

   A Member State may request assistance from another Member State or from the Agency.

3. The supervisory authority for pharmacovigilance shall be the competent authority of the Member State in which the pharmacovigilance system master file is located.

Article 51

Responsibilities of the supervisory authorities

1. The supervisory authorities for manufacturing and imports shall be responsible for verifying on behalf of the Union that the marketing authorisation holder for the medicinal product or the manufacturer or importer established within the Union satisfies the requirements concerning manufacturing and imports laid down in Chapters XI and XV of [revised Directive 2001/83/EC].

   When carrying out the verification referred to in the first subparagraph, the supervisory authorities may request to be accompanied by a rapporteur or expert appointed by the Committee for Medicinal Products for Human Use or by an inspector of the Agency.

   The supervisory authorities for pharmacovigilance shall be responsible for verifying on behalf of the Union that the marketing authorisation holder for the medicinal product satisfies the pharmacovigilance requirements laid down in Chapters IX and XV of [revised Directive 2001/83/EC].

   The supervisory authorities for pharmacovigilance may, if necessary, conduct pre-authorisation inspections to verify the accuracy and successful implementation of the pharmacovigilance system as it has been described by the applicant in support of their application.

2. Where, in accordance with Article 202 of [revised Directive 2001/83/EC], the Commission is informed of serious differences of opinion between Member States as to whether the marketing authorisation holder for the medicinal product for human use or a manufacturer or importer established within the Union satisfies the requirements referred to in paragraph 1, the Commission may, after consultation with the Member States concerned, request an inspector from the supervisory authority to undertake a new inspection of the marketing authorisation holder, the manufacturer or the importer.

   The inspector in question shall be accompanied by two inspectors from Member States which are not party to the dispute or by two experts nominated by the Committee for Medicinal Products for Human Use.

3. Taking into account any agreements which may have been concluded between the Union and third countries in accordance with Article 50, the Commission may, following a reasoned request from a Member State or from the Committee for Medicinal Products for Human Use, or on its own initiative, require a manufacturer established in a third country to submit to an inspection.

The inspection shall be undertaken by inspectors from the Member States who possess the appropriate qualifications. They may request to be accompanied by a rapporteur or expert appointed by the Committee for Medicinal Products for Human Use or by an inspector of the Agency. The report of the inspectors shall be made available electronically to the Commission, the Member States and the Agency.

Article 52

Inspection capacity of the Agency

1. When an inspection, included in the system of supervision referred to in Article 188(1), point (a) of [revised Directive 2001/83/EC] is requested, as referred to in Article 11(2), for a site located in a third country, the supervisory authority for this site may request the Agency to participate in the inspection or to carry out the inspection.

2. The Agency, following a request in accordance with paragraph 1, may decide either of the following:

   (a) to lend its assistance by participating in a joint inspection with the supervisory authority of the site. In that case the supervisory authority leads the inspection and the follow up thereof. After completion of the inspection, the supervisory authority grants the relevant good manufacturing practice (GMP) certificate and enters the certificate in the Union database; or

   (b) to carry out the inspection and the follow up thereof on behalf of the supervisory authority. After completion of the inspection, the Agency grants the relevant GMP certificate and enters the certificate in the Union database referred to in Article 188(15) of [revised Directive 2001/83/EC].

   Where the Agency decides to carry out the inspection, the Agency may request other Member States to participate in the inspection. To any such request, the provisions on joint inspections of Article 189 of [revised Directive 2001/83/EC] shall apply. In case the Agency carries out the inspection in form of a joint inspection, the Agency leads the inspection.

   The Agency may also request to be accompanied by a rapporteur or expert appointed by the Committee for Medicinal Products for Human Use.

   Where a follow-up inspection is required in view of a non-compliance GMP certificate issued by the Agency, the supervisory authority of the site will be in charge of its performance; the procedure of paragraph 2 shall apply if the supervisory authority for this site requests the Agency to participate in the follow up inspection or to take over the performance of the inspection.

3. The Agency shall take into account the criteria set out in Annex III when taking its decision in accordance with paragraph 2.

4. Article 188, paragraph 6, and paragraphs 8 to 17 of [revised Directive 2001/83/EC] shall apply to the inspections referred to in paragraph 2.

The Agency's inspectors shall have the same powers conferred on official representatives of the competent authority pursuant to these provisions.

5. Following a request by a Member State, the inspectors of the Agency may provide support to such Member State when it performs inspections referred to in Article 78 of Regulation (EU) 536/2014. The Agency shall take a decision whether to carry out itself such inspection based on the criteria set out in Annex III.

6. The Agency shall ensure that

(a) appropriate resources are made available for the performance of inspection tasks in accordance with the paragraphs 2 and 5;

(b) the inspectors of the Agency possess expertise, technical knowledge, and formal qualifications equivalent to those of the national inspectors as detailed in the compilation, published by the Commission, on Union procedures on inspections and exchange of information.

(c) it participates as an inspectorate in the Joint Audit Programme and be subjected to periodic audits.

Article 53

International Inspections

1. The Agency shall in consultation with the Commission, coordinate a structured cooperation on inspections in third countries between Member States, and as relevant the European Directorate for the Quality of Medicines and Healthcare of the Council of Europe, the World Health Organisation and trusted international authorities, by means of international inspection programmes.

2. In cooperation with the Agency, the Commission may adopt detailed guidelines laying down the principles applicable to those international inspection programmes.

Article 54

Joint Audit Programme

1. The inspection working group referred to in Article 142, point (k), shall ensure the following:

(a) establish and develop the joint audit programme ('JAP') and supervise it;

(b) monitor any measure taken by the Member State pursuant and limited to paragraph 4;

(c) ensure cooperation with relevant international and Union level bodies to facilitate the work of the joint audit programme.

For the purposes of the first subparagraph, the inspection working group may establish an operational subgroup.

2. For the purposes of paragraph 1, point (a), each Member State shall:

(a) provide trained auditors;

(b) accept that the competent authority in charge of the implementation of good manufacturing and good distribution practice and related surveillance and enforcement activities applicable to medicinal products and active substances

are audited, regularly and where appropriate, according to the joint audit programme.

3. The joint audit programme shall be considered an integral part of the quality system of the inspectorates referred to in Article 3(3) of Commission Directive (EU) 2017/1572[35] and ensure that adequate and equivalent quality standards are maintained within the Union network of national competent authorities.

4. Under the joint audit programme, the auditors shall issue an audit report after each audit. The audit report shall include, where relevant, appropriate recommendations on measures that the Member State concerned shall consider to take to ensure that its relevant quality system and its enforcement activities are consistent with Union quality standards.

   At the request of the Member State, the Commission or the Agency may support that Member State in taking the appropriate measures pursuant to the first subparagraph.

5. For the purposes of paragraph 4, the Agency shall:

   (a) ensure the quality and consistency of the joint audit programme's audit reports;

   (b) establish the criteria for the provision of the joint audit programme's recommendations.

6. The compilation of Union procedures on inspections and exchange of information referred to in Article 3(1) of Directive 2017/1572 shall be updated by the Agency to cover rules applicable to the functioning, structure, and tasks of the joint audit programme.

7. The Union shall provide the financing for activities that support the work of the joint audit programme.

Article 55

Referral procedure

1. Where the supervisory authorities or the competent authorities of any other Member State are of the opinion that the manufacturer or importer established within the Union territory is no longer fulfilling the obligations laid down in Chapter XI of [revised Directive 2001/83/EC], they shall without undue delay inform the Agency and the Commission, stating their reasons in detail and indicating the course of action proposed.

   Similarly, where a Member State or the Commission considers that one of the measures envisaged in Chapters IX, XIV and XV of [revised Directive 2001/83/EC] is to be applied in respect of the medicinal product concerned or where the Committee for Medicinal Products for Human Use has delivered an opinion to that effect, they shall without undue delay inform each other, as well as the Committee for Medicinal Products of Human Use, stating their reasons in detail and indicating the course of action proposed.

2. In each of the situations described in paragraph 1, the Commission shall request the opinion of the Agency within a time-limit which it shall determine having regard to

[35] Commission Directive (EU) 2017/1572 of 15 September 2017 supplementing Directive 2001/83/EC of the European Parliament and of the Council as regards the principles and guidelines of good manufacturing practice for medicinal products for human use (OJ L 238, 16.9.2017, p. 44).

the urgency of the matter, in order to examine the reasons advanced. Whenever practicable, the marketing authorisation holder for placing the medicinal product for human use on the market shall be invited to provide oral or written explanations.

3. At any stage of the procedure laid down in this Article, following appropriate consultation of the Agency, the Commission may take temporary measures, by means of implementing acts. Those temporary measures shall be applied immediately.

Without undue delay, the Commission shall, by means of implementing acts, adopt a final decision concerning the measures to be taken in respect of the medicinal product concerned. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 173(2).

The Commission may also, pursuant to Article 57, adopt a decision addressed to the Member States.

4. Where urgent action is essential to protect public health or the environment, a Member State may, on its own initiative or at the Commission's request, suspend the use in its territory of a medicinal product for human use which has been authorised in accordance with this Regulation.

When it does so on its own initiative, it shall inform the Commission and the Agency of the reasons for its action at the latest on the next working day following the suspension. The Agency shall inform the other Member States without delay. The Commission shall immediately initiate the procedure provided for in paragraphs 2 and 3.

5. In cases referred to in paragraph 4, the Member State shall ensure that healthcare professionals are rapidly informed of its action and the reasons for the action. Networks set up by professional associations may be used to this effect. The Member States shall inform the Commission and the Agency of actions taken for this purpose.

6. The suspensive measures referred to in paragraph 4 may be maintained in force until such time as a final decision has been adopted by the Commission in accordance with paragraph 3.

7. The Agency shall, upon request, inform any person concerned of the final decision and make the decision publicly available immediately after it has been taken.

8. Where the procedure is initiated as a result of the evaluation of data relating to pharmacovigilance, the opinion of the Agency, in accordance with paragraph 2, shall be adopted by the Committee for Medicinal Products for Human Use on the basis of a recommendation from the Pharmacovigilance Risk Assessment Committee and Article 115(2) of [revised Directive 2001/83/EC] shall apply.

9. By way of derogation from paragraphs 1 to 7, where a procedure under Article 95 or Articles 114, 115 and 116 of [revised Directive 2001/83/EC] concerns a range of medicinal products or a therapeutic class, medicinal products that are authorised in accordance with this Regulation and that belong to that range or class shall only be included in the procedure under Article 95, or Articles 114, 115 and 116 of that Directive.

Article 56

Action on conditional marketing authorisation

Where the Agency concludes that a holder of a marketing authorisation granted in accordance with Article 19, including a new therapeutic indication granted referred to Article 19, failed to comply with the obligations laid down in the marketing authorisation, the Agency shall inform the Commission accordingly.

The Commission shall adopt a decision to vary, suspend or revoke that marketing authorisation in accordance with the procedure set out in Article 13.

Article 57

Member State implementation of conditions or restrictions on a Union marketing authorisation

When the Committee for Medicinal Products for Human Use in its opinion refers to recommended conditions or restrictions as provided for in Article 12(4), points (d) to (g), the Commission may adopt a decision addressed to the Member States, in accordance with Article 13 for the implementation of those conditions or restrictions.

CHAPTER V
PRE-AUTHORISATION REGULATORY SUPPORT

Article 58

Scientific advice

1. Undertakings or, as relevant, not-for-profit entities may request scientific advice as referred to in Article 138(1), second subparagraph, point (p) , from the Agency.

   Such advice can also be requested for medicinal products referred to in Articles 83 and 84 of [revised Directive 2001/83/EC].

2. In the preparation of the scientific advice referred to in paragraph 1 and upon request by undertakings or, as relevant, not-for-profit entities that requested the scientific advice, the Agency may consult experts of the Member States with clinical trial or medical device expertise or the expert panels designated in accordance with Article 106(1) of Regulation (EU) 2017/745.

3. In the preparation of the scientific advice referred to in paragraph 1 and in duly justified cases, the Agency may consult authorities established in other Union legal acts as relevant for the provision of the scientific advice in question or other public bodies established in the Union, as applicable.

4. The Agency shall include in the European public assessment report the key areas of the scientific advice once the corresponding marketing authorisation decision has been taken in relation to the medicinal product, after deletion of any information of a commercially confidential nature.

Article 59

Parallel scientific advice

1. Undertakings or, as relevant, not-for-profit entities established in the Union may request that the scientific advice referred to in Article 58(1) takes place in parallel to the joint scientific consultation carried out by the Member State Coordination Group on Health Technology Assessment, in line with Article 16(5) of Regulation (EU) 2021/2282.

2. In case of medicinal products involving a medical device, undertakings or, as relevant, not-for-profit entities may request scientific advice as referred to in Article 58(1) in parallel with the consultation of the expert panels referred to in Article 61(2) of Regulation (EU) 2017/745.

3. In the case of paragraph 2, the scientific advice, as referred to in Article 58(1), shall involve exchanges of information between the respective authorities or bodies and, where applicable, have synchronised timing, while preserving the separation of their respective remits.

Article 60

Enhanced scientific and regulatory support for priority medicinal products ('PRIME')

1. The Agency may offer enhanced scientific and regulatory support, including as applicable consultation with other bodies as referred to in Articles 58 and 59 and accelerated assessment mechanisms, for certain medicinal products that, based on preliminary evidence submitted by the developer fulfil the following conditions:

   (a) are likely to address an unmet medical need as referred to in Article 83(1) of [revised Directive 2001/83/EC];

   (b) are orphan medicinal products and are likely to address a high unmet medical need as referred to in Article 70(1);

   (c) are expected to be of major interest from the point of view of public health, in particular as regards therapeutic innovation, taking into account the early stage of development, or antimicrobials with any of the characteristics mentioned in Article 40(3).

2. The Agency, at the request of the Commission and after consulting the EMA Emergency Task Force, may offer enhanced scientific and regulatory support to developers of a medicinal product preventing, diagnosing or treating a disease resulting from serious cross border threats to health if access to such products is considered necessary to ensure high level of Union preparedness and response to health threats.

3. The Agency may stop the enhanced support if it is established that the medicinal product will not address the identified unmet medical need to the anticipated extent.

4. The compliance of a medicinal product with the criteria set out in Article 83 of [revised Directive 2001/83/EC] shall be assessed on the basis of the relevant criteria, independently of whether it has received priority medicinal product support under this Article.

Article 61

Scientific recommendation on regulatory status

1. For products under development which may fall within the categories of medicinal products to be authorised by the Union listed in Annex I, a developer or a competent authority of the Member States may submit a duly substantiated request to the Agency for a scientific recommendation with a view to determining on scientific grounds whether the concerned product is potentially a 'medicinal product',

including an ‘advanced therapy medicinal product’ as defined in Article 2 of Regulation (EC) No 1394/2007 of the European Parliament and of the Council[36].

The Agency shall deliver its recommendation within 60 days of receiving such a request, which shall be extended by an additional 30 days where a consultation in accordance with paragraph 2 is required.

2. When forming the recommendation referred to in paragraph 1, the Agency shall consult, where appropriate, relevant advisory or regulatory bodies established in other Union legal acts in related fields. In the case of products which are based on substances of human origin, the Agency shall consult the Substances of Human Origin (SoHO) Coordination Board as established in Regulation (EU) No [*reference to be added after adoption cf. COM(2022)338 final*].

The advisory or regulatory bodies consulted shall reply to the consultation within 30 days of receipt of the request.

The Agency shall publish summaries of the recommendations delivered in accordance with paragraph 1, after deletion of all information of a commercially confidential nature.

Article 62

Decision on regulatory status

1. In the case of duly substantiated disagreement with the Agency’s recommendation, in accordance with Article 61(2), a Member State may request the Commission to decide whether the product is a product referred to in Article 61(1).

The Commission may initiate the procedure referred to in the first subparagraph on its own initiative.

2. The Commission may ask the Agency for clarifications or refer the recommendation back to the Agency for further consideration where a Member State's substantiated request raises new questions of a scientific or technical nature or on its own initiative.

3. The decision of the Commission referred to in paragraph 1 shall be adopted by means of implementing acts, in accordance with the examination procedure referred to in Article 173(2), taking into account the scientific recommendation of the Agency.

CHAPTER VI
ORPHAN MEDICINAL PRODUCTS

Article 63

Criteria for orphan designation

1. A medicinal product that is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition shall be designated as an orphan

[36] Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (OJ L 324, 10.12.2007, p. 121).

medicinal product where the orphan medicine sponsor can demonstrate that the following requirements are met:

(a) the condition affects not more than five in 10 000 persons in the Union when the application for an orphan designation is submitted;

(b) there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Union or, where such method exists, that the medicinal product would be of significant benefit to those affected by that condition.

2. By way of derogation from paragraph 1, point (a), and on the basis of a recommendation from the Agency, when the requirements specified in paragraph 1, point (a), are not appropriate due to the specific characteristics of certain conditions or any other scientific reasons, the Commission is empowered to adopt delegated acts in accordance with Article 175 in order to supplement paragraph 1, point (a), by setting specific criteria for certain conditions.

3. The Commission shall adopt the necessary provisions for implementing this Article by means of implementing acts in accordance with the procedure laid down in Article 173(2) in order to further specify the requirements referred to in paragraph 1.

Article 64

Granting an orphan designation

1. The orphan medicine sponsor shall submit an application for the designation of the orphan medicinal product to the Agency at any stage of the development of the medicinal product before the application for marketing authorisation referred to in Articles 5 and 6 is submitted.

2. The application of the orphan medicine sponsor shall be accompanied by the following particulars and documentation:

(a) name or corporate name and permanent address of the orphan medicine sponsor;

(b) active substances of the medicinal product;

(c) proposed condition for which it is intended or the proposed therapeutic indication;

(d) justification that the criteria laid down in Article 63(1) or in the relevant delegated acts adopted in accordance with Article 63(2) are fulfilled and a description of the stage of development, including the expected therapeutic indication.

The orphan medicine sponsor shall be responsible for the accuracy of the particulars and documentation.

3**.** The Agency shall, in consultation with the Member States, the Commission and interested parties, draw up detailed guidelines on the required procedure, format and content of applications for designation and for the transfer of the orphan designation pursuant to Article 65.

4. The Agency shall adopt a decision granting or refusing the orphan designation based on the criteria referred to in Article 63(1) or in the relevant delegated acts adopted in accordance with Article 63(2) within 90 days of the receipt of a valid application.

The application is considered valid if it includes all the particulars and documentation referred to in paragraph 2.

For the purpose of establishing whether the orphan designation criteria are fulfilled, the Agency may consult the Committee for Medicinal Products for Human Use or one of its working parties referred to in Article 150(2), first subparagraph. The outcome of such consultations shall be annexed to the decision, as part of the scientific conclusions of the Agency which justify the decision.

The decision together with the Annexes referred to in this paragraph shall be notified to the applicant.

5. Decisions of the Agency on granting or refusing the orphan designation shall be made public after deletion of any information of a commercially confidential nature.

Article 65

Transfer of orphan designation

1. The orphan designation may be transferred from a current orphan medicine sponsor to a new orphan medicine sponsor. The transfer shall be subject to prior approval by the Agency, following the submission of an application for the transfer to the Agency.

2. The application of the current orphan medicine sponsor shall be accompanied by the following particulars and documentation:

   (a) name or corporate name and permanent address of the current and new orphan medicine sponsor;

   (b) decision on granting an orphan designation as referred to in Article 64(4);

   (c) designation number as referred to in Article 67(3), point (e).

3 The Agency shall adopt a decision granting or refusing the transfer of the orphan designation within 30 days of the receipt of a valid application by the current orphan medicine sponsor. The application is considered valid if it includes all the particulars and documentation referred to in paragraph 2. The Agency shall address its decision to the current and new orphan medicine sponsor.

Article 66

Validity of orphan designation

1. An orphan designation shall be valid for seven years. During this period, the orphan medicine sponsor shall be eligible for incentives referred to in Article 68.

2. By way of derogation from paragraph 1, on the basis of a justified request of the orphan medicine sponsor, the Agency may extend the validity, where the orphan medicine sponsor can provide evidence that the relevant studies supporting the use of the designated orphan medicinal product in the applied conditions are ongoing and promising with regard to the filing of a future application. Such an extension shall be limited in time, taking into account the expected remaining time needed to file an application for marketing authorisation.

3. By way of derogation from paragraph 1, where an orphan designation is valid at the time when a marketing authorisation for an orphan medicinal product has been

submitted in accordance with Article 5, the orphan designation shall remain valid until a decision is adopted by the Commission in accordance with Article 13(2).

4. An orphan designation ceases to be valid once an orphan medicine sponsor has obtained a marketing authorisation for the relevant medicinal product in accordance with Article 13(2).

5. At any time, an orphan designation may be withdrawn at the request of the orphan medicine sponsor.

Article 67

Register of designated orphan medicinal products

1. The register of designated orphan medicinal products shall list all designated orphan medicinal products. It shall be set up and managed by the Agency and be publicly available.

2. Where an orphan designation ceases to be valid or is withdrawn pursuant to Article 66, the Agency shall make an entry in the register of designated orphan medicinal products.

3. The information on the designated orphan medicinal product entered in the register of designated orphan medicinal products shall include at least the following:

   (a) the information on the active substance;

   (b) the name and address of the orphan medicine sponsor;

   (c) the condition for which it is intended or the proposed therapeutic indication;

   (d) the designation date;

   (e) the designation number;

   (f) the decision on granting the orphan designation.

4. The Commission shall be empowered to adopt delegated acts in accordance with Article 175 in order to amend the information to be included in the register of designated orphan medicinal products referred to in paragraph 3 to ensure appropriate information of the users of that register.

Article 68

Protocol assistance and research support for orphan medicinal products

1. The orphan medicine sponsor may, prior to the submission of an application for marketing authorisation, request advice from the Agency on the following:

   (a) the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of the medicinal product, as referred to Article 138(1), second subparagraph, point (p);

   (b) the demonstration of significant benefit within the scope of the designated orphan indication;

   (c) the demonstration of similarity to or clinical superiority over other medicinal products, which have market exclusivity for the same indication.

2. Medicinal products designated as orphan medicinal products under the provisions of this Regulation shall be eligible for incentives made available by the Union and by

the Member States to support research into, and the development and availability of, orphan medicinal products and in particular aid for research for small- and medium-sized undertakings provided for in framework programmes for research and technological development.

Article 69

Orphan marketing authorisation

1. Applications for an orphan marketing authorisation shall be submitted in accordance with Articles 5 and 6 and the related marketing authorisation shall be obtained in accordance with Articles 13(2).

2. In addition, the applicant shall demonstrate that the medicinal product has been granted an orphan designation and that the criteria set out in Article 63(1) or in the relevant delegated acts adopted in accordance with Article 63(2) are fulfilled for the therapeutic indication sought.

   Where appropriate, the applicant shall provide relevant evidence to demonstrate that the medicinal product addresses a high unmet medical need as specified in Article 70(1).

3. The Committee for Medicinal Products for Human Use shall assess whether the medicinal product fulfils the requirements set out in Article 63(1) or in the relevant delegated acts adopted in accordance with Article 63(2). In the situation referred in paragraph 2, subparagraph 2, that Committee shall also assess whether the medicinal product addresses a high unmet medical need as specified in Article 70(1).

   Such assessment shall be subject to the same timelines as the application for the marketing authorisation itself and detailed conclusions of such assessment shall be part of the scientific opinion of the Committee for Medicinal Products for Human Use in accordance with Article 12(1).

   The assessment and its conclusions shall be part of the opinion referred to in Article 12(1) and, where relevant, the opinion referred to in Article 12(3).

5. The orphan marketing authorisation shall cover only those therapeutic indications, which fulfil the requirements set out in Article 63(1) or in the relevant delegated acts adopted in accordance with Article 63(2) at the time when the orphan marketing authorisation is granted.

6. If after the submission of an application for the orphan marketing authorisation and prior to the opinion of the Committee for Medicinal Products for Human Use the orphan designation is withdrawn in accordance with Article 66(5), the application for the orphan marketing authorisation shall be treated as the application for a marketing authorisation in accordance with Article 6.

7. An applicant may submit an application for a separate marketing authorisation for other indications which do not fulfil the requirements set out in Article 63(1) or in the relevant delegated acts adopted in accordance with Article 63(2).

Article 70

Orphan medicinal products addressing a high unmet medical need

1. An orphan medicinal product shall be considered as addressing a high unmet medical need where it fulfils the following requirements:

(a) there is no medicinal product authorised in the Union for such condition orwhere, despite medicinal products being authorised for such condition in the Union, the applicant demonstrates that the orphan medicinal product, in addition to having a significant benefit, will bring exceptional therapeutic advancement;

(b) the use of the orphan medicinal product results in a meaningful reduction in disease morbidity or mortality for the relevant patient population.

2. A medicinal product for which an application has been submitted in accordance with Article 13 of [revised Directive 2001/83/EC] shall not be considered as addressing a high unmet medical need.

3. Where the Agency adopts scientific guidelines for the application of this Article, it shall consult the Commission and the authorities or bodies referred to in Article 162.

Article 71

Market exclusivity

1. Where an orphan marketing authorisation is granted and without prejudice to intellectual property law, the Union and the Member States shall not grant a marketing authorisation or extend an existing marketing authorisation, for the same therapeutic indication, in respect of a similar medicinal product for the duration of market exclusivity set out in paragraph 2.

2. The duration of market exclusivity shall be as follows:

(a) nine years for orphan medicinal products other than those referred to in points (b) and (c);

(b) ten years for orphan medicinal products addressing a high unmet medical need as referred to in Article 70;

(c) five years for orphan medicinal products which have been authorised in accordance with Article 13 of [revised Directive 2001/83/EC].

3. Where a marketing authorisation holder holds more than one orphan marketing authorisations for the same active substance, those authorisations shall not benefit from separate market exclusivity periods. The duration of the market exclusivity shall start from the date when the first orphan marketing authorisation was granted in the Union.

4. By way of derogation from paragraph 1, and without prejudice to intellectual property law, the marketing authorisation may be granted, for the same therapeutic indication, to a similar medicinal product if:

(a) the marketing authorisation holder for the original orphan medicinal product has given consent to the second applicant, or

(b) the marketing authorisation holder for the original orphan medicinal product is unable to supply sufficient quantities of the medicinal product, or

(c) the second applicant can establish in the application that the second medicinal product, although similar to the orphan medicinal product already authorised, is safer, more effective or otherwise clinically superior.

5. The submission, validation and assessment of the application for the marketing authorisation and granting the marketing authorisation for a generic or biosimilar

product to the reference medicinal product for which market exclusivity has expired, shall not be prevented by the market exclusivity of a similar product to the reference medicinal product.

6. The market exclusivity of the orphan medicinal product shall not prevent the submission, validation and assessment of an application for a marketing authorisation for a similar medicinal product, including generics and biosimilars, where the remainder of the duration of the market exclusivity is less than two years.

7. Where the Agency adopts scientific guidelines for the application of paragraphs 1 and 4, it shall consult the Commission.

Article 72

Prolongation of market exclusivity

1. The periods of market exclusivity referred to in Article 71, paragraph 2, points (a) and (b), shall be prolonged by 12 months, where the orphan marketing authorisation holder can demonstrate that the conditions referred to in Article 81(2), point (a), and Article 82(1) [of revised Directive 2001/83/EC] are fulfilled.

   The procedures set out in Articles 82(2) to (5) [of revised Directive 2001/83/EC] shall accordingly apply to the prolongation of market exclusivity.

2. The period of market exclusivity shall be prolonged by an additional 12 months for orphan medicinal products referred to in Article 71(2), points (a) and (b), if at least two years before the end of the exclusivity period, the orphan marketing authorisation holder obtains a marketing authorisation for one or more new therapeutic indications for a different orphan condition.

   Such a prolongation may be granted twice, if the new therapeutic indications are each time for different orphan conditions.

3. The orphan medicinal products which benefit from the prolongation of market exclusivity referred to in the paragraph 2 shall not benefit from the additional period of data protection referred to in Article 81(2), point (d), of [revised Directive 2001/83/EC].

4. Article 71(3) equally applies to the prolongations of market exclusivity referred to in paragraphs 1 and 2.

Article 73

Union financial contribution related to orphan medicinal products

The working arrangements referred to in Article 8 of [new fee Regulation][37] shall set out total or partial reductions for the applicable fees and charges payable to the European Medicines Agency as laid down in [new fee Regulation]. Such reductions shall be covered by the Union contribution provided for in Article 154(3), point (a) of this Regulation.

[37] Regulation [XXX] of the European Parliament and of the Council on fees and charges payable to the European Medicines Agency, amending Regulation (EU) 2017/745 of the European Parliament and of the Council and repealing Council Regulation (EC) No 297/95 and Regulation (EU) 658/2014 of the European Parliament and of the Council [OJ L X, XX.XX.XXXX, p. X].

CHAPTER VII
PAEDIATRIC MEDICINAL PRODUCTS

Article 74

Paediatric investigation plan

1. A paediatric investigation plan shall specify the timing and all the measures proposed to assess the quality, safety and efficacy of the medicinal product in all subsets of the paediatric population that may be concerned. In addition, it shall describe any measures to adapt the pharmaceutical form, the strength, the route of administration and the eventual administration device of the medicinal product so as to make its use more acceptable, easier, safer or more effective for different subsets of the paediatric population.

2. By derogation from paragraph 1, in the following cases an applicant may submit only an initial paediatric investigation plan as referred to in the second subparagraph:

   (a) when the active substance concerned is not yet authorised in any medicinal product in the EU and is intended to treat a novel paediatric condition;

   (b) following the acceptance by the Agency of a justified request from an applicant in accordance with paragraph 3.

   An initial paediatric investigation plan shall contain only the details and the timing of the measures proposed to assess the quality, safety and efficacy of the medicinal product in all subsets of the paediatric population that may be concerned, that are known at the moment of the submission of the request for agreement mentioned in Article 76(1).

   This initial paediatric investigation plan shall also provide a precise timing of when updated versions of the paediatric investigation plan are to be submitted and when a final paediatric investigation plan complying with all the particulars described in paragraph 1, is expected to be submitted to the Agency.

3. When it is not possible, on the basis of scientifically justified reasons, to have a complete paediatric development plan in accordance with the timing given in Article 76(1) an applicant may submit a justified request to the Agency to utilise the procedure mentioned in paragraph 2. The Agency has 20 days to accept or refuse the request and shall immediately inform the applicant and state the reasons for refusal.

4. On the basis of the experience acquired as a result of the operation of this Article or of scientific knowledge, the Commission is empowered to adopt delegated acts in accordance with Article 175 to amend the grounds for granting the possibility to utilise the adapted procedure foreseen in paragraph 2.

Article 75

Waivers

1. In accordance with the procedure set out in Article 78, the Agency may decide that the production of the information referred to in, Article 6(5), point (a), of [revised Directive 2001/83], shall be waived for products or for classes of medicinal products, if there is evidence showing any of the following:

(a) that the specific medicinal product or class of medicinal products is likely to be ineffective or unsafe in part or all of the paediatric population;

(b) that the disease or condition for which the specific medicinal product or class is intended occurs only in adult populations, unless when the product is directed at a molecular target that on the basis of existing scientific data, is responsible for a different disease or condition in the same therapeutic area in children than the one for which the specific medicinal product or class of medicinal products is intended for in the adult population;

(c) that the specific medicinal product is likely to not represent a significant therapeutic benefit over existing treatments for paediatric patients.

2. The waiver provided for in paragraph 1 may be issued with reference either to one or more specified subsets of the paediatric population, or to one or more specified therapeutic indications, or to a combination of both.

3. On the basis of the experience acquired as a result of the operation of this Article or of scientific knowledge the Commission is empowered to adopt delegated acts in accordance with Article 175 to amend the grounds for granting a waiver detailed in paragraph 1.

Article 76

Validation of a paediatric investigation plan or of a waiver

1. A paediatric investigation plan or an application for waiver shall be submitted to the Agency with a request for agreement, except in duly justified cases, before the initiation of safety and efficacy clinical studies so as to ensure that a decision on use in the paediatric population of the medicinal product concerned can be given at the time of the marketing authorisation or other application concerned.

2. Within 30 days following receipt of the request referred to in paragraph 1, the Agency shall verify the validity of the request and communicate the result to the applicant.

3. Whenever appropriate, the Agency may ask the applicant to submit additional particulars and documents, in which case the time-limit of 30 days shall be suspended until the supplementary information requested has been provided.

4. In consultation with the Commission and with interested parties, the Agency shall draw up and publish guidelines for the practical application of this Article.

Article 77

Agreement on a paediatric investigation plan

1. After the validation of the proposed paediatric investigation plan referred to in Article 74(1).which is valid in accordance with the provisions of Article 76(2), the Agency shall adopt within 90 days a decision as to whether or not the proposed studies will ensure the generation of the necessary data determining the conditions in which the medicinal product may be used to treat the paediatric population or subsets thereof, and as to whether or not the expected therapeutic benefits, where appropriate also over existing treatments, justify the studies proposed. When adopting its decision, the Agency shall consider whether or not the measures proposed to adapt the pharmaceutical form, the strength, the route of administration and the eventual

administration device of the medicinal product for use in different subsets of the paediatric population are appropriate.

2. After the validation of the proposed initial paediatric investigation plan prepared in accordance with the adapted procedure referred to in Article 74(2) first subparagraph, which is valid in accordance with the provisions of Article 76(2), the Agency shall adopt a decision within 70 days as to whether or not the paediatric investigation plan is expected to ensure the generation of the necessary data determining the conditions in which the medicinal product may be used to treat the paediatric population or subsets thereof, and as to whether or not the expected therapeutic benefits, where appropriate also over existing treatments, justify the studies envisaged.

3. After receiving an updated version of the paediatric investigation plan referred to in Article 74(2), third subparagraph, the Agency shall review it within 30 days.

   After the timeframe laid down in the first subparagraph, without any request from the Agency in accordance with paragraph 5, the updated version of the paediatric investigation plan shall be considered as agreed.

4. When the final paediatric investigation plan referred to in Article 74(2), third subparagraph, is received, the Agency shall adopt within 60 days a decision on the paediatric investigation plan considering all the updated reviews eventually conducted and of the initial decision in accordance with paragraphs 2 and 3.

5. Within time periods referred to in paragraphs 1, 2, 3 or 4 the Agency may request the applicant to propose modifications to the plan or ask for additional information, in which case the time-limits referred to in paragraphs 1, 2, 3 and 4 shall be extended for a maximum of the same number of days. These time-limits shall be suspended until the supplementary information requested has been provided.

6. The procedure laid down in Article 87 shall apply for the adoption of decisions by the Agency.

Article 78

Granting of a waiver

1. An applicant may, on the grounds set out in Article 75(1), apply to the Agency for a product-specific waiver.

2. Following the receipt of a valid application in accordance with the provisions of Article 76(2), the Agency shall within 90 days adopt a decision as to whether or not a product-specific waiver shall be granted.

   Whenever appropriate, the Agency may request the applicant to supplement the particulars and documents submitted. Where the Agency avails itself of this option, the 90-day time-limit shall be suspended until such time as the supplementary information requested has been provided.

3. When appropriate, the Agency may of its own motion adopt decisions, on the basis of the grounds set out in Article 75(1), to the effect that a class or a product-specific waiver, as referred to in Article 75(2), should be granted.

4. The Agency may, at any time adopt a decision reviewing an already granted waiver.

5. If a particular product-specific or class waiver is revoked, the requirement set out in Article 6(5) of [revised Directive 2001/83/EC] shall not apply for 36 months from the date of its removal from the list of waivers.

6. The procedure laid down in Article 87 shall apply for the adoption of decisions by the Agency.

7. In consultation with the Commission and with interested parties, the Agency shall draw up and publish guidelines for the practical application of this Article.

Article 79

List of waivers

The Agency shall maintain a list of all waivers granted. The list shall be updated regularly and made available to the public.

Article 80

Waivers granted following a negative decision on a paediatric investigation plan

If, having considered a paediatric investigation plan, the Agency concludes that Article 75(1), points (a), (b) or (c), applies to the medicinal product concerned, it shall adopt negative a decision under Article 77, paragraphs 1, 2 or 4.

In such cases, the Agency shall adopt a decision in favour of a waiver under Article 78(3). The two decisions shall be adopted at the same time by the Agency.

The procedure laid down in Article 87 shall apply for the adoption of decisions by the Agency.

Article 81

Deferrals

1. At the same time as the application for a paediatric investigation plan is submitted under Article 76(1) or during the assessment for a paediatric investigation plan, the applicant may also make a request for deferral of the initiation or completion of some or all of the measures set out in that plan. Such deferral shall be justified on scientific and technical grounds or on grounds related to public health.

   In any event, a deferral shall be granted when it is appropriate to conduct studies in adults prior to initiating studies in the paediatric population or when studies in the paediatric population will take longer to conduct than studies in adults.

2. The Agency shall adopt a decision on the request referred to in paragraph 1 and inform the applicant thereof. The Agency shall adopt such decision at the same time as the adoption of the positive decision under Article 77, paragraphs 1 or 2.

   A decision in favour of a deferral shall specify the time-limits for initiating or completing the measures concerned.

3. The length of the deferral shall be specified in a decision of the Agency and shall not exceed five years.

4. On the basis of the experience acquired as a result of the operation of this Article, the Commission is empowered to adopt delegated acts in accordance with Article 175 to amend the grounds for granting a deferral referred to in paragraph 1.

Article 82

Prolongation of deferrals

1. In duly justified cases, a request for a prolongation of the deferral, may be submitted, at least 6 months before the expiry of the deferral period. A prolongation of the derogation shall not exceed the duration of the deferral period given under Article 81(3).

   The Agency shall decide on the prolongation within 60 days.

2. Whenever appropriate, the Agency may ask the applicant to submit additional particulars and documents, in which case the time-limit of 60 days shall be suspended until the supplementary information requested has been provided.

3. The procedure laid down in Article 87 shall apply for the adoption of decisions by the Agency.

Article 83

Waivers during a public health emergency

1. The decision by the Agency referred to in Article 6(5), point (e) of [revised Directive 2001/83/EC] shall concern only medicinal products intended for the treatment, prevention or medical diagnosis of a serious or life-threatening disease or condition which are directly related to the public health emergency.

2. The decision mentioned under paragraph 1 shall include the grounds for providing such derogation and its duration.

3. At the latest at the date of expiry of the derogation referred to in paragraph 2, the applicant shall submit to the Agency a paediatric investigation plan or an application for a waiver with a request for agreement in accordance with the provisions of Article 76(1).

Article 84

Modification of a paediatric investigation plan

1. If, following the decision agreeing the paediatric investigation plan, the applicant encounters such difficulties with its implementation as to render the plan unworkable or no longer appropriate, the applicant may propose changes or request the Agency to issue a deferral in accordance with Article 81 or a waiver in accordance with Article 75. The Agency shall adopt within 90 days a decision on the basis of the procedure laid down in Article 87. When appropriate, the Agency may request the applicant to supplement the particulars and documents submitted. Where the Agency avails itself of this option, the time-limit shall be suspended until such time as the supplementary information requested has been provided.

2. If, following the decision agreeing the paediatric investigation plan referred to in Article 77, paragraphs 1, 2 and 4, or on the basis of the updated paediatric investigation plan received in accordance with Article 77(3), the Agency, on the base of new scientific information available, considers that the agreed plan or any of its elements are no longer appropriate, it shall request the applicant to propose changes to the paediatric investigation plan.

   The applicant shall submit the changes requested within 60 days.

Within 30 days, the Agency shall review these changes and adopt a decision on their refusal or acceptance.

3. Within the time period referred to in paragraph 2, third subparagraph, the Agency may request the applicant for additional modifications to the submitted changes or to submit additional information, in those cases the time-limits referred to in paragraph 2, third subparagraph, shall be extended by another 30 days. This time-limit shall be suspended until the supplementary information requested or the additional modifications have been provided.

4. The procedure laid down in Article 87 shall apply for the adoption of decisions by the Agency.

Article 85

Detailed arrangements for applications in relation to paediatric investigation plans, waivers and deferrals

1. In consultation with the Member States, the Commission and interested parties, the Agency shall draw up the detailed arrangements concerning the format and content which applications for agreement or modification of a paediatric investigation plan, and requests for waivers or deferrals are to follow in order to be considered valid and concerning the operation of the compliance check referred to in Articles 48, 49(2), 86 and 90(2) of [revised Directive 2001/83/EC].

2. The detailed arrangement concerning the format and content of applications for agreement of a paediatric investigation plan mentioned in paragraph 1 shall:

   (a) specify which information should be included in an application for agreement or modification of a paediatric investigation plan or requests for a waiver in the cases referred to in Article 75(1);

   (b) be adapted to take into account the specificities of:

      (i) adapted procedure for paediatric investigation plans as referred to in Article 74(2);

      (ii) products intended to be developed only for use in children;

      (iii) products intended to be submitted under the procedure referred to in Article 92.

Article 86

Compliance with the paediatric investigation plan

Where the application is submitted in accordance with the procedures set out in in this Regulation, the Committee for Medicinal Products for Human Use shall verify whether an application for marketing authorisation or variation complies with the requirements laid down in Article 6(5) of [revised Directive 2001/83/EC].

Article 87

Procedure for adopting a decision in relation to paediatric investigation plans, a waiver or a deferral

1. Decisions referred to in Articles 77, 78, 80, 81, 82 and 84 adopted by the Agency shall be supported by scientific conclusions which shall be annexed to the decision.

2. Where the Agency considers it necessary, it may consult the Committee for Medicinal Products for Human Use or the appropriate working parties when preparing the above mentioned scientific conclusions. The outcome of such consultations shall be annexed to the decision.

3. Decisions of the Agency shall be made public after deletion of any information of a commercially confidential nature.

Article 88

Discontinuation of a paediatric investigation plan

Where a paediatric investigation plan, agreed in accordance with the provisions of Article 77, paragraphs 1, 2 and 4, is discontinued, the applicant shall notify the Agency of its intention to discontinue the conduct of the paediatric investigation plan and provide the reasons for such discontinuation no less than six months before the discontinuation.

The Agency shall publish this information.

Article 89

Scientific advice for paediatric developments

Any legal or natural person developing a medicinal product intended for paediatric use or intended for in utero treatment may, prior to the submission of a paediatric investigation plan and during its implementation, request advice from the Agency on the design and conduct of the various tests and studies necessary to demonstrate the quality, safety and efficacy of the medicinal product in the paediatric population in accordance with Article 138(1), point (za).

The Agency shall provide advice under this Article free of charge.

Article 90

Data deriving from a paediatric investigation plan

1. Where a marketing authorisation or a variation of a marketing authorisation, is granted in accordance with this Regulation:

   (a) the results of all clinical studies conducted in compliance with an agreed paediatric investigation plan as referred to in Articles 6(5), point (a), of [revised Directive 2001/83/EC] shall be included in the summary of product characteristics and, if appropriate, in the package leaflet; or

   (b) any agreed waiver as referred to in Articles 6(5), points (b) and (c) of [revised Directive 2001/83/EC], shall be recorded in the summary of product characteristics and, if appropriate, in the package leaflet of the medicinal product concerned.

2. If the application complies with all the measures contained in the agreed completed paediatric investigation plan and if the summary of product characteristics reflects the results of studies conducted in compliance with that agreed paediatric investigation plan, the Commission shall include within the marketing authorisation a statement indicating compliance of the application with the agreed completed paediatric investigation plan.

Article 91

Variation of marketing authorisations on the basis of paediatric studies

1. Any clinical study which involves the use in the paediatric population of a medicinal product covered by a marketing authorisation and is sponsored by the marketing authorisation holder, whether or not it is conducted in compliance with an agreed paediatric investigation plan, shall be submitted to the Agency or to the Member States which have previously authorised the medicinal product concerned within six months of completion of the studies concerned.

2. Paragraph 1 shall apply independent of whether or not the marketing authorisation holder intends to apply for a marketing authorisation of a paediatric indication.

3. When products are authorised in accordance with the provisions of this Regulation, the Commission may update the summary of product characteristics and package leaflet, and may vary the marketing authorisation accordingly.

Article 92

Paediatric use marketing authorisation

1. An application for a paediatric use marketing authorisation shall be submitted in accordance with Articles 5 and 6 and shall be accompanied by the particulars and documents necessary to establish quality, safety and efficacy in the paediatric population, including any specific data needed to support an appropriate formulation, pharmaceutical form, strength, route of administration and eventual administration device for the product, in accordance with an agreed paediatric investigation plan. The application shall also include the decision of the Agency agreeing the paediatric investigation plan concerned.

2. Where a medicinal product is or has been authorised in a Member State or in the Union, data contained in the dossier on that product may, where appropriate, be referred to, in accordance with Article 29 or Article 9 of [revised Directive 2001/83/EC], in an application for a paediatric use marketing authorisation.

3. The medicinal product in respect of which a paediatric use marketing authorisation is granted may retain the name of any medicinal product which contains the same active substance and in respect of which the same marketing authorisation holder has been granted authorisation for use in adults.

4. Submission of an application for a paediatric use marketing authorisation shall in no way preclude the right to apply for a marketing authorisation for other therapeutic indications.

Article 93

Rewards for products authorised under the paediatric use marketing authorisation procedure

Where a paediatric use marketing authorisation referred to in Article 92 is granted and includes the results of all studies conducted in compliance with an agreed paediatric investigation plan, the product shall benefit from independent data and marketing protection periods referred to in Articles 80 and 81 of [revised Directive 2001/83/EC].

Article 94

Paediatric clinical trials

1. The EU database created by Article 81 of Regulation (EU) No 536/2014 shall include clinical trials carried out in third countries which are:

   (a) contained in an agreed paediatric investigation plan;

   (b) submitted following the provisions of Article 91.

2. For the clinical trials mentioned in paragraph 1 which are conducted in third countries, the description of the following elements shall be entered into the EU database prior to the start of the trial by the clinical trial sponsor, the addressee of the Agency's decision on a paediatric investigation plan referred to in Article 77, or by the marketing authorisation holder as appropriate:

   (a) the clinical trial protocol;

   (b) the investigational medicinal products used;

   (c) the therapeutic indications covered;

   (d) details of the trial population.

   Irrespective of the outcome of a clinical trial within 6 months from the end of the trial the clinical trial sponsor, the addressee of the Agency's decision on a paediatric investigation plan or the marketing authorisation holder as appropriate, shall submit to the EU database a summary of the results of the trial shall be uploaded in the database.

   If for justified scientific reasons it is not possible to submit the summary of the result of the trial within 6 months it shall be submitted to the EU database at the latest within twelve months after the trial has ended. The justification for the delay needs also to be submitted in the EU database.

3. In consultation with the Commission, Member States and interested parties, the Agency shall draw up guidance on the nature of the information referred to in paragraph 2.

4. On the basis of the experience acquired as a result of the operation of this Article, the Commission may adopt implementing acts in accordance with the examination procedure referred to in Article 173(2) to amend the details concerning clinical trials conducted in third countries to be submitted to the EU database and referred to in paragraph 2.

Article 95

European network

1. The Agency shall develop a European network of patient representatives, academics, medicines developers, investigators and centres with expertise in the performance of studies in the paediatric population.

2. The objectives of the European network shall be, inter alia, to discuss priorities in the clinical development of medicines for children, in particular in areas of unmet medical need, to coordinate studies relating to paediatric medicinal products, to build up the necessary scientific and administrative competences at European level, and to avoid unnecessary duplication of studies and testing in the paediatric population.

Article 96

Incentives for research in medicinal products for children

Paediatric medicinal products shall be eligible for incentives made available by the Union and by the Member States to support research into, and the development and availability of, paediatric medicinal products.

Article 97

Fees and Union contribution for paediatric activities

1. Where an application for a paediatric use marketing authorisation is submitted in accordance with the procedure laid down in Article 92, the amount of the reduced fees for the examination of the application and the maintenance of the marketing authorisation shall be fixed in accordance with Article 6 of [new fee Regulation[38]].

2. Assessments of the following by the Agency shall be free of charge:

   (a) applications for waivers;

   (b) applications for deferrals;

   (c) applications for paediatric investigation plans;

   (d) compliance with the agreed paediatric investigation plan.

3. The Union contribution provided for in Article 154 shall cover the work of the Agency, including the assessment of paediatric investigation plans, scientific advice and any fee waivers provided for in this Chapter, and shall support the Agency's activities under Articles 94 and 95.

Article 98

Yearly reporting

At least on an annual basis, the Agency shall make public:

(a) a list of the companies and of the products that have benefited from any of the rewards and incentives in this Regulation;

(b) the companies that have failed to comply with any of the obligations in this Regulation;

(c) the number of paediatric investigation plans agreed in accordance with Article 74;

(d) the number of waivers agreed, providing also a summary of their reasons;

(e) a list of deferrals agreed;

(f) the number of paediatric investigation plans completed;

(g) the renewals of the deferrals beyond five years and the detailed reasons provided as mentioned in Article 82;

[38] Regulation [XXX] of the European Parliament and of the Council on fees and charges payable to the European Medicines Agency, amending Regulation (EU) 2017/745 of the European Parliament and of the Council and repealing Council Regulation (EC) No 297/95 and Regulation (EU) 658/2014 of the European Parliament and of the Council [OJ L X, XX.XX.XXXX, p. X].

(h) the scientific advice provided for the development of medicinal products addressed to children.

CHAPTER VIII
PHARMACOVIGILANCE

Article 99

Pharmacovigilance

1. The obligations of marketing authorisation holders laid down in Articles 99 and 100(1) of [revised Directive 2001/83/EC] shall apply to marketing authorisation holders for medicinal products for human use authorised in accordance with this Regulation.

2. The Agency may impose an obligation on a holder of a centralised marketing authorisation to operate a risk management system, as referred to in Article 99(4), point (c) of [revised Directive 2001/83/EC], if there are concerns about the risks affecting the benefit-risk balance of an authorised medicinal product. In that context, the Agency shall also oblige the marketing authorisation holder to submit a risk management plan for the risk-management system that they intend to introduce for the medicinal product concerned.

   The obligation referred to in paragraph 2 shall be duly justified, notified in writing, and shall include the timeframe for submission of the risk-management plan.

3. The Agency shall provide the marketing authorisation holder with an opportunity to submit written observations in response to the imposition of the obligation within a time limit which it shall specify, if the marketing authorisation holder so requests within 30 days of receipt of the written notification of the obligation.

   On the basis of the written observations submitted by the marketing authorisation holder, the Agency shall review its opinion.

4. Where the opinion of the Agency confirms the obligation and unless the Commission returns the opinion to the Agency for further consideration, the marketing authorisation shall be varied accordingly by the Commission in accordance with the procedure set out in Article 13, to:

   (a) include the obligation as a condition of the marketing authorisation and the risk management system shall be updated accordingly.

   (b) include the measures to be taken as part of the risk management system as conditions of the marketing authorisation referred to in Article 12(4), point (e).

Article 100

Safety announcements

The obligations of marketing authorisation holders laid down in Article 104(1) of [revised Directive 2001/83/EC], and the obligations of the Member States, the Agency and the Commission laid down in paragraphs 2, 3 and 4 of that Article shall apply to the safety announcements referred to in Article 138(1), point (f), of this Regulation concerning medicinal products for human use authorised in accordance with this Regulation.

Article 101

Eudravigilance database

1. The Agency shall, in collaboration with the Member States and the Commission, set up and maintain a database and data processing network ('Eudravigilance database') to collate pharmacovigilance information regarding medicinal products authorised in the Union and to allow competent authorities to access that information simultaneously and to share it.

   In justified cases, the Eudravigilance database may include pharmacovigilance information with regard to medicinal products used under compassionate use referred to in Article 26 or early access schemes.

   The Eudravigilance database shall contain information on suspected adverse reactions in human beings arising from use of the medicinal product within the terms of the marketing authorisation as well as from uses outside the terms of the marketing authorisation, and on those occurring in the course of post-authorisation studies with the medicinal product or associated with occupational exposure.

2. The Agency shall, in collaboration with the Member States and the Commission, draw up the functional specifications for the Eudravigilance database, together with a timeframe for their implementation.

   The Agency shall prepare an annual report on the Eudravigilance database and send it to the European Parliament, the Council and the Commission.

   Any substantial change to the Eudravigilance database and the functional specifications shall take into account the recommendations of the Pharmacovigilance Risk Assessment Committee.

   The Eudravigilance database shall be fully accessible to the competent authorities of the Member States and to the Agency and the Commission. It shall also be accessible to marketing authorisation holders to the extent necessary for them to comply with their pharmacovigilance obligations.

   The Agency shall ensure that healthcare professionals and the public have appropriate levels of access to the Eudravigilance database, and that personal data is protected. The Agency shall work together with all stakeholders, including research institutions, healthcare professionals, and patient and consumer organisations, in order to define the 'appropriate level of access' for healthcare professionals and the public to the Eudravigilance database.

   The data held on the Eudravigilance database shall be made publicly available in an aggregated format together with an explanation of how to interpret the data.

3. The Agency shall, in collaboration either with the marketing authorisation holder or with the Member State that submitted an individual suspected adverse reaction report to the Eudravigilance database, be responsible for operating procedures that ensure the quality and integrity of the information collected in the Eudravigilance database.

4. Individual suspected adverse reaction reports and follow-ups submitted to the Eudravigilance database by marketing authorisation holders shall be transmitted electronically upon receipt to the competent authority of the Member State where the reaction occurred.

Article 102

Forms for reporting suspected adverse reactions

The Agency shall, in collaboration with the Member States, develop standard web-based structured forms for the reporting of suspected adverse reactions by healthcare professionals and patients in accordance with the provisions referred to in Article 106 of [revised Directive 2001/83/EC].

Article 103

Periodic safety update reports repository

The Agency shall, in collaboration with the competent authorities of the Member States and the Commission, set up and maintain a repository for periodic safety update reports ('repository') and the corresponding assessment reports regarding medicinal products authorised in the Union so that they are fully and permanently accessible to the Commission, the competent authorities of the Member States, the Pharmacovigilance Risk Assessment Committee, the Committee for Medicinal Products for Human Use and the coordination group referred to in Article 37 of [revised Directive 2001/83/EC] ('coordination group').

The Agency shall, in collaboration with the competent authorities of the Member States and the Commission, and after consultation with the Pharmacovigilance Risk Assessment Committee, draw up the functional specifications for the repository.

Any substantial change to the repository and the functional specifications shall always take into account the recommendations of the Pharmacovigilance Risk Assessment Committee.

Article 104

European medicines web-portal and register of studies for environmental risk assessment

1. The Agency shall, in collaboration with the Member States and the Commission, set up and maintain a European medicines web-portal for the dissemination of information on medicinal products authorised or to be authorised in the Union. By means of that portal, the Agency shall make public the following:

   (a) the names of members of the Committees referred to in Article 142, points (d) and (e), and the members of the coordination group, together with their professional qualifications and with the declarations referred to in Article 147(2);

   (b) agendas and minutes from each meeting of the Committees referred to in Article 142, points (d) and (e), and of the coordination group as regards pharmacovigilance activities;

   (c) a summary of the risk management plans for medicinal products authorised in accordance with this Regulation;

   (d) a list of the locations in the Union where pharmacovigilance system master files are kept and contact information for pharmacovigilance enquiries, for all medicinal products authorised in the Union;

   (e) information about how to report to competent authorities of the Member States suspected adverse reactions to medicinal products and the standard structured forms referred to in Article 102 for their web-based reporting by patients and healthcare professionals, including links to national websites;

(f) Union reference dates and frequency of submission of periodic safety update reports established in accordance with Article 108 of [revised Directive 2001/83/EC];

(g) protocols and public abstracts of results of the post-authorisation safety studies referred to in Articles 108 and 120 of [revised Directive 2001/83/EC];

(h) the initiation of the procedure provided for in Article 41(2), and Articles 114, 115 and 116 of [revised Directive 2001/83/EC], the active substances or medicinal products concerned and the issue being addressed, any public hearings pursuant to that procedure and information on how to submit information and to participate in public hearings;

(i) conclusions of assessments, recommendations, opinions, approvals and decisions taken by the Agency and its Committees under this Regulation and [revised Directive 2001/83/EC], unless it is required that this information is made public by the Agency by other means;

(j) conclusions of assessments, recommendations, opinions, approvals and decisions taken by the coordination group, the competent authorities of the Member States and the Commission in the framework of the procedures set out in Articles 16, 106, 107 and 108 of this Regulation and of Chapter IX, Sections 3 and 7 of [revised Directive 2001/83/EC].

The summaries referred to in point (c) shall include a description of any additional risk minimisation measures.

2. In the development and review of the web portal, the Agency shall consult relevant stakeholders, including patient and consumer groups, healthcare professionals and industry representatives.

3. The Agency shall, in collaboration with the Member States and the Commission, set up and maintain a register of environmental risk assessment studies conducted for the purpose of supporting an environmental risk assessment for medicinal products authorised in the Union, unless such information is made public in the Union by different means.

Information in such register shall be publicly available, unless restrictions are necessary to protect commercially confidential information. For the purpose of setting up such register, the Agency may request marketing authorisation holders and competent authorities to submit results of any such study already completed for products authorised in the Union within [*OP please add the date = 24 months after the date of application of this Regulation*].

Article 105

Literature monitoring

1. The Agency shall monitor selected medical literature for reports of suspected adverse reactions to medicinal products containing certain active substances. It shall publish the list of active substances being monitored and the medical literature subject to this monitoring.

2. The Agency shall enter into the Eudravigilance database relevant information from the selected medical literature.

3. The Agency shall, in consultation with the Commission, Member States and interested parties, draw up a detailed guide regarding the monitoring of medical literature and the entry of relevant information into the Eudravigilance database.

Article 106

Monitoring of safety of medicinal products

1. The obligations of marketing authorisation holders and of Member States laid down in Article 105 and Article 106 of [revised Directive 2001/83/EC] shall apply to the recording and reporting of suspected adverse reactions for medicinal products for human use authorised in accordance with this Regulation.

2. The obligations of marketing authorisation holders laid down in Article 107 of [revised Directive 2001/83/EC] and the procedures under Articles 107 and 108 of that Directive shall apply to the submission of periodic safety update reports, the establishment of Union reference dates and changes to the frequency of submission of periodic safety update reports for medicinal products for human use authorised in accordance with this Regulation.

   The provisions applicable to the submission of periodic safety update reports laid down in the of Article 108(2), second subparagraph, of that Directive shall apply to marketing authorisation holders of marketing authorisations which were granted before 2 July 2012 and for which the frequency and dates of submission of the periodic safety update reports are not laid down as a condition to the marketing authorisation until such time as another frequency or other dates of submission of the reports are laid down in the marketing authorisation or are determined in accordance with Article 108 of that Directive.

3. The assessment of the periodic safety update reports shall be conducted by a rapporteur appointed by the Pharmacovigilance Risk Assessment Committee. The rapporteur shall closely collaborate with the rapporteur appointed by the Committee for Medicinal Products for Human Use or the Reference Member State for the medicinal products concerned.

   The rapporteur shall prepare an assessment report within 60 days of receipt of the periodic safety update report and send it to the Agency and to the members of the Pharmacovigilance Risk Assessment Committee. The Agency shall send the report to the marketing authorisation holder.

   Within 30 days of receipt of the assessment report, the marketing authorisation holder and the members of the Pharmacovigilance Risk Assessment Committee may submit comments to the Agency and to the rapporteur.

   Following the receipt of the comments referred to in the third subparagraph, the rapporteur shall within 15 days update the assessment report taking into account any comments submitted, and forward it to the Pharmacovigilance Risk Assessment Committee. The Pharmacovigilance Risk Assessment Committee shall adopt the assessment report with or without further changes at its next meeting and issue a recommendation. The recommendation shall mention the divergent positions with the grounds on which they are based. The Agency shall include the adopted assessment report and the recommendation in the repository set up under Article 103, and forward both to the marketing authorisation holder.

4. In the case of an assessment report that recommends any action concerning the marketing authorisation, the Committee for Medicinal Products for Human Use shall, within 30 days of receipt of the report by the Pharmacovigilance Risk Assessment Committee, consider the report and adopt an opinion on the maintenance, variation, suspension or revocation of the marketing authorisation concerned, including a timetable for the implementation of the opinion. Where this opinion of the Committee for Medicinal Products for Human Use differs from the recommendation of the Pharmacovigilance Risk Assessment Committee, the Committee for Medicinal Products for Human Use shall attach to its opinion a detailed explanation of the scientific grounds for the differences together with the recommendation.

   Where the opinion states that regulatory action concerning the marketing authorisation is necessary, the Commission shall adopt a decision, by means of implementing acts, to vary, suspend or revoke the marketing authorisation in accordance with Article 13. Where the Commission adopts such a decision, it may also adopt a decision addressed to the Member States pursuant to Article 57.

5. In the case of a single assessment of periodic safety update reports concerning more than one marketing authorisation in accordance with Article 110(1) of [revised Directive 2001/83/EC] which includes at least one marketing authorisation granted in accordance with this Regulation, the procedure laid down in Article 107 and Article 109 of that Directive shall apply.

6. The final recommendations, opinions and decisions referred to in paragraphs 3, 4 and 5 shall be made public by means of the European medicines web-portal referred to in Article 104.

Article 107

Agency pharmacovigilance related activities

1. Regarding medicinal products for human use authorised in accordance with this Regulation, the Agency shall, in collaboration with the Member States, take the following measures:

   (a) monitor the outcome of risk minimisation measures contained in risk management plans and of conditions referred to in Article 12, paragraph 4, points (d) to (g), or in Article 20, paragraph 1, points (a) and (b), and in Articles 18(1) and 19;

   (b) assess updates to the risk management system;

   (c) monitor the data in the Eudravigilance database to determine whether there are new risks or whether risks have changed and whether those risks impact on the benefit-risk balance.

2. The Pharmacovigilance Risk Assessment Committee shall perform the initial analysis and prioritisation of signals of new risks or risks that have changed or changes to the benefit-risk balance. Where it considers that follow-up action may be necessary, the assessment of those signals and agreement on any subsequent action concerning the marketing authorisation shall be conducted in a timescale commensurate with the extent and seriousness of the issue. Where appropriate, the assessment of those signals may be included in a pending assessment of a periodic safety update report or a pending procedure in accordance with Articles 95 and 114 of [revised Directive 2001/83/EC] or Article 55 of this Regulation.

3. The Agency and competent authorities of the Member States and the marketing authorisation holder shall inform each other in the event of new risks or risks that have changed or changes to the benefit-risk balance being detected.

Article 108

Non-interventional post-authorisation safety studies

1. For non-interventional post-authorisation safety studies concerning medicinal products for human use authorised in accordance with this Regulation which have been imposed in accordance with Articles 13 and 20, the procedure provided for in Article 117, paragraphs 3 to 7, Articles 118, 119, 120 and 121(1) of [revised Directive 2001/83/EC] shall apply.

2. Where, in accordance with the procedure referred to in paragraph 1, the Pharmacovigilance Risk Assessment Committee issues recommendations for the variation, suspension or revocation of the marketing authorisation, the Committee on Medicinal Products for Human Use shall adopt an opinion taking into account the recommendation, and the Commission shall adopt a decision in accordance with Article 13.

   Where the opinion of the Committee for Medicinal Products for Human Use differs from the recommendation of the Pharmacovigilance Risk Assessment Committee, the Committee for Medicinal Products for Human Use shall attach to its opinion a detailed explanation of the scientific grounds for the differences, together with the recommendation.

Article 109

Exchange of information with other organisations

1. The Agency shall collaborate with the World Health Organization in matters of pharmacovigilance and shall take the necessary steps to submit to it, promptly, appropriate and adequate information regarding the measures taken in the Union which could have a bearing on public health protection in third countries.

   The Agency shall make available promptly all suspected adverse reaction reports occurring in the Union to the World Health Organization.

2. The Agency and the European Monitoring Centre for Drugs and Drug Addiction shall exchange information that they receive on the abuse of medicinal products including information related to illicit drugs.

Article 110

International collaboration

At the request of the Commission, the Agency shall participate in collaboration with the Member States in international harmonisation and standardisation of technical measures in relation to pharmacovigilance.

Article 111

Cooperation with Member States

The Agency and the Member States shall cooperate to continuously develop pharmacovigilance systems capable of achieving high standards of public health protection for all medicinal products, regardless of the routes of marketing authorisation, including the use of collaborative approaches, to maximise use of resources available within the Union.

Article 112

Reports on pharmacovigilance tasks

The Agency shall perform regular independent audits of its pharmacovigilance tasks and report the results to its Management Board on a 2-yearly basis. The results shall be subsequently published.

CHAPTER IX
REGULATORY SANDBOX

Article 113

Regulatory sandbox

1. The Commission may set up a regulatory sandbox pursuant to a specific sandbox plan, based on a recommendation of the Agency and pursuant to the procedure set out in paragraphs 4 to 7, where all the following conditions are met:

   (a) it is not possible to develop the medicinal product or category of products in compliance with the requirements applicable to medicinal products due to scientific or regulatory challenges arising from characteristics or methods related to the product;

   (b) the characteristics or methods referred to in point (a) positively and distinctively contribute to the quality, safety or efficacy of the medicinal product or category of products or provide a major advantage contribution to patient access to treatment.

2. The regulatory sandbox shall set out a regulatory framework, including scientific requirements, for the development and, where appropriate clinical trials and placing on the market of a product referred to in paragraph 1 under the conditions set out in this Chapter. The regulatory sandbox may allow targeted derogations to this Regulation, [revised Directive 2001/83/EC] or Regulation (EC) 1394/2007 under the conditions set out in Article 114.

   A regulatory sandbox shall take effect under direct supervision of the competent authorities of the Member States concerned with a view to ensuring compliance with the requirements of this Regulation and, where relevant, other Union and Member State legislation concerned by the sandbox. Any violation of the conditions set out in the decision referred to in paragraph 6 and the identification of any risks to health and to environment shall be immediately notified to the Commission and to the Agency.

3. The Agency shall monitor the field of emerging medicinal products and may request information and data from marketing authorisation holders, developers, independent experts and researchers, and representatives of healthcare professionals and of patients and may engage with them in preliminary discussions.

4. Where the Agency considers it appropriate to set up a regulatory sandbox for medicinal products which are likely to fall under the scope of this Regulation, it shall provide a recommendation to the Commission. The Agency shall list eligible products or category of products in that recommendation and shall include the sandbox plan referred to in paragraph 1.

   The Agency shall not recommend to set up a regulatory sandbox for a medicinal product that is already advanced in its development programme.

5. The Agency shall be responsible for developing a sandbox plan based on data submitted by developers of eligible products and following appropriate consultations. The plan shall set out clinical, scientific and regulatory justification for a sandbox, including the identification of the requirements of this Regulation, [revised Directive 2001/83/EC] and Regulation (EC) 1394/2007 that cannot be complied with and a proposal for alternative or mitigation measures, where appropriate. The plan shall also include a proposed timeline for the duration of the sandbox. Where appropriate, the Agency shall also propose measures in order to mitigate any possible distortion of market conditions as a consequence of establishing a regulatory.

6. The Commission shall, by means of implementing acts, take a decision on the set up of a regulatory sandbox taking into account the recommendation of the Agency and the sandbox plan pursuant to paragraph 4. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 173(2).

7. Decisions establishing a regulatory sandbox under paragraph 5 shall be limited in time and shall set out detailed conditions for its implementation. These Decisions shall:

   (a) include the proposed sandbox plan;

   (b) include the duration of the regulatory sandbox and its expiry;

   (c) include as part of the sandbox plan the requirements of this Regulation and of [revised Directive 2001/83/EC] that cannot be complied with and shall include appropriate measures to mitigate potential risks to health and to the environment.

8. The Commission may, by means of implementing acts, suspend or revoke a regulatory sandbox at any time. in any of the following cases:

   (a) the requirements and conditions laid down in paragraphs 6 and 7 are no longer met;

   (b) it is appropriate to protect public health.

   Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 173(2).

   Where the Agency receives information that one of the cases referred to in the first subparagraph may be fulfilled, it shall inform the Commission accordingly.

9. Where after the Decision to establish the regulatory sandbox in accordance with paragraph 6, risks to health are identified but these risks can be fully mitigated by the adoption of supplementary conditions, the Commission may, after consultation of the Agency, amend its decision by means of implementing acts. The Commission may also prolong the duration of a regulatory sandbox by means of implementing acts. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 173(2).

10. This Article shall not exclude the setting up of time limited pilot projects to test different ways of implementing the applicable legislation.

Article 114

Products developed under a sandbox

1. When authorising a clinical trial application for products covered by a regulatory sandbox, Member States shall take the sandbox plan referred to in Article 113(1) into consideration.

2. A medicinal product developed as part of a regulatory sandbox may be placed on the market only when authorised in accordance with this Regulation. The initial validity of such authorisation shall not exceed the duration of the regulatory sandbox. The authorisation may be prolonged at the request of the marketing authorisation holder.

3. In duly justified cases, the marketing authorisation of a medicinal product developed under the regulatory sandbox may include derogations from the requirements set out in this Regulation and [revised Directive 2001/83/EC]. Those derogations may entail adapted, enhanced, waived or deferred requirements. Each derogation shall be limited to what is apt and strictly necessary to attain the objectives pursued, duly justified and specified in the conditions to the marketing authorisation.

4. For medicinal products developed as part of a regulatory sandbox for which a marketing authorisation has been granted in accordance with paragraph 2 and where appropriate paragraph 3, the summary of product characteristics and the package leaflet shall indicate that the medicinal product has been developed as part of a regulatory sandbox.

5. Without prejudice to Article 195 of [revised Directive 2001/83/EC], the Commission shall suspend a marketing authorisation granted in accordance with paragraph 2, where the regulatory sandbox has been suspended or revoked in accordance with Article 113(7).

6. The Commission shall immediately vary the marketing authorisation to take account of the mitigation measures taken in accordance with Article 115.

Article 115

General sandbox provisions

1. The regulatory sandboxes shall not affect the supervisory and corrective powers of the competent authorities. In case of identification of risks to public health or safety concerns associated with the use of products covered by a sandbox, competent authorities shall take immediate and adequate temporary measures in order to suspend or restrict their use and inform the Commission in accordance with Article 113(2).

   Where such mitigation is not possible or proves to be ineffective, the development and testing process shall be suspended without delay until an effective mitigation takes place.

2. Participants in the regulatory sandbox, in particular the marketing authorisation holder of the medicinal product concerned, shall remain liable under applicable Union and Member States liability legislation for any harm inflicted on third parties as a result from the testing taking place in the sandbox. They shall inform the

Agency without undue delay of any information which might entail the amendment of the regulatory sandbox or concerns the quality, safety or efficacy of products developed as part of a regulatory sandbox.

3. The modalities and the conditions of the operation of the regulatory sandboxes, including the eligibility criteria and the procedure for the application, selection, participation and exiting from the sandbox, and the rights and obligations of the participants shall be set out in implementing acts. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 173(2).

4. The Agency with input from Member States shall submit annual reports to the Commission on the results from the implementation of a regulatory sandbox, including good practices, lessons learnt and recommendations on their setup and, where relevant, on the application of this Regulation and other Union legal acts supervised within the sandbox. These reports shall be made publicly available by the Commission.

5. The Commission shall review the reports and put forward, as appropriate, legislative proposals with a view to update the regulatory framework referred to in Article 113(2) or delegated acts in accordance with Article 28 of [revised Directive 2001/83/EC].

CHAPTER X
AVAILABILITY AND SECURITY OF SUPPLY OF MEDICINAL PRODUCTS

SECTION 1

MONITORING AND MANAGEMENT OF SHORTAGES AND CRITICAL SHORTAGES

Article 116

Marketing authorisation holder notifications

1. The marketing authorisation holder of a medicinal product in possession of a centralised marketing authorisation or a national marketing authorisation (‘the marketing authorisation holder’) shall notify the competent authority of the Member State where the medicinal product has been placed on the market and, in addition, the Agency for a medicinal product covered by a centralised marketing authorisation (these are referred to in this Chapter as ‘the competent authority concerned’) of the following:

   (a) its decision to permanently cease the marketing of a medicinal product in that Member State no less than twelve months before the last supply of that medicinal product into the market of a given Member State by the marketing authorisation holder;

   (b) its request to permanently withdraw the marketing authorisation for that medicinal product authorised in that Member State no less than twelve months before the last supply of that medicinal product into the market of a given Member State by the marketing authorisation holder;

(c) its decision to temporarily suspend the marketing of a medicinal product in that Member State no less than six months before the start of the temporary suspension of supply of that medicinal product into the market of a given Member State by the marketing authorisation holder;

(d) a temporary disruption in supply of a medicinal product in a given Member State, of an expected duration of in excess of two weeks or, based on the demand forecast of the marketing authorisation holder no less than six months before the start of such temporary disruption of supply or, if this is not possible and where duly justified, as soon as they become aware of such temporary disruption, to allow the Member State to monitor any potential or actual shortage in accordance with Article 118(1).

2. For the purposes of the notification made in accordance with paragraph 1, points (a), (b) and (c), the marketing authorisation holder shall provide the information set out in Part I of Annex IV.

For the purpose of notifications made in accordance with the paragraph 1, point (d), the marketing authorisation holder shall provide the information set out in Part III of Annex IV.

The marketing authorisation holder shall immediately notify the competent authority concerned, as appropriate, of any relevant changes to the information provided according to this paragraph.

3. The Commission is empowered to adopt delegated acts, in accordance with Article 175 in order to amend Annex IV as regards the information to be provided in case of a temporary disruption of supply, information to be provided in case of a suspension or cessation of marketing of a medicinal product or withdrawal of the marketing authorisation of a medicinal product, or the content of the shortage prevention plan referred to in Article 117.

Article 117

The shortage prevention plan

1. The marketing authorisation holder as defined in Article 116(1) shall have in place and keep up to date a shortage prevention plan, for any medicinal product placed on the market. To put in place the shortage prevention plan, the marketing authorisation holder shall include the minimum set of information set out in Part V of Annex IV and take into account the guidance drawn up by the Agency according to paragraph 2.

2. The Agency, in collaboration with the working party referred to in Article 121(1), point (c), shall draw up guidance to marketing authorisation holders as defined in Article 116(1) to put in place the shortage prevention plan.

3. Where relevant, the marketing authorisation holder as defined in Article 116(1) shall update the shortage prevention plan to include additional information, based on recommendations of the Executive Steering Group on Shortages and Safety of Medicinal Products (also referred to as the Medicine Shortages Steering Group – 'MSSG', established in Article 3(1) of Regulation (EU) 2022/123, in accordance with Articles 123(4) and 132(1).

Article 118

Shortage monitoring by the competent authority of the Member State or the Agency

1. Based on the reports referred to in Articles 120(1) and 121(1), point (c), information referred to in Articles 119, 120(2) and 121 and the notification made pursuant to Article 116(1), points (a) to (d), the competent authority concerned as referred to in Article 116(1) shall continuously monitor any potential or actual shortage of those medicinal products.

   The Agency shall carry out that monitoring in collaboration with the relevant competent authority of the Member State when those medicinal products are authorised under this Regulation.

2. For the purposes of paragraph 1, the competent authority concerned as defined in Article 116(1) may request any additional information from the marketing authorisation holder as defined in Article 116(1). In particular, it may request the marketing authorisation holder to submit a shortage mitigation plan in accordance with Article 119(2), a risk assessment of impact of suspension, cessation or withdrawal in accordance with Article 119(3), or the shortage prevention plan referred to in Article 117. The competent authority concerned may set a deadline for the submission of the information requested.

Article 119

Obligations on the marketing authorisation holder

1. The marketing authorisation holder as defined in Article 116(1) shall:

   (a) submit the information requested in accordance with Article 118(2) or Article 124(2), point (b) to the competent authority concerned as defined in Article 116(1), without undue delay, using the tools, methods of and criteria for the monitoring and reporting established pursuant to Article 122(4), point (b), by the deadline set by that competent authority;

   (b) provide updates to the information provided in accordance with point (a), where necessary;

   (c) justify any failure to provide any of the requested information;

   (d) where necessary, submit a request to the competent authority concerned as defined in Article 116(1) for an extension of the deadline set by that competent authority in accordance with point (a), and

   (e) indicate whether the information provided in accordance with point (a) contains any commercially confidential information, identify the relevant parts of that information having a commercially confidential nature and explain why that information is of such nature.

2. To prepare the shortage mitigation plan referred to in Article 118(2), the marketing authorisation holder as defined in Article 116(1) shall include the minimum set of information set out in Part IV of Annex IV and take into account the guidance drawn up by the Agency according to Article 122(4), point (c).

3. To prepare a risk assessment of impact of suspension, cessation or withdrawal referred to in Article 118(2), the marketing authorisation holder as defined in Article 116(1) shall include the minimum set of information set out in Part II of Annex IV

and take into account the guidance drawn up by the Agency according to Article 122(4), point (c).

4. The marketing authorisation holder as defined in Article 116(1) shall be responsible for providing correct, not misleading, and complete information as requested by the competent authority concerned.

5. The marketing authorisation holder as defined in Article 116(1) shall cooperate with that competent authority and disclose, on their own motion, any relevant information to that authority and update the information as soon as new information becomes available.

Article 120

Obligations on other actors

1. Wholesale distributors and other persons or legal entities that are authorised or entitled to supply medicinal products authorised to be placed on the market of a Member State pursuant to Article 5 of [revised Directive 2001/83/EC] to the public may report a shortage of a given medicinal product marketed in the Member State concerned to the competent authority in that Member State.

2. For the purposes of Article 118(1), where relevant, upon request from the competent authority concerned as defined in Article 116(1), entities including other marketing authorisation holders as defined in Article 116(1), importers and manufacturers of medicinal products or active substances and relevant suppliers of these, wholesale distributors, stakeholder representative associations or other persons or legal entities that are authorised or entitled to supply medicinal products to the public shall provide any information requested in a timely manner.

Article 121

Role of the competent authority of the Member State

1. The competent authority of the Member State shall:

   (a) assess the merits of each confidentiality claim made by the marketing authorisation holder as defined in Article 116(1) in accordance with Article 119(1), point (e), and shall protect information which that competent authority considers to be commercially confidential against unjustified disclosure;

   (b) publish information on actual shortages of medicinal products, in cases in which that competent authority has assessed the shortage, on a publicly available website;

   (c) report to the Agency, through the single point of contact working party referred to in Article 3(6) of Regulation (EU) 2022/123, any shortage of a medicinal product that it identifies as a critical shortage in that Member State to the Agency without undue delay.

2. Following the reporting referred to in paragraph 1, point (c), and to facilitate the monitoring referred to in Articles 118(1), the competent authority of the Member State shall, through the working party referred to in paragraph 1, point (c):

   (a) submit to the Agency the information referred to in Articles 122(1) or 124(2), point (a), using the tools, methods of and criteria for the monitoring and

reporting established pursuant to Article 122(4), point (b), by the deadline set by the Agency;

(b) where necessary, provide updates to the information provided in accordance with point (a) to the Agency;

(c) justify any failure to provide any of the information referred to in point (a) to the Agency;

(d) where necessary, submit a request to the Agency to extend the deadline set by the Agency referred to in point (a);

(e) indicate whether the marketing authorisation holder as defined in Article 116(1) has indicated the existence of any commercially confidential information and provide the marketing authorisation holder's explanation of why that information is of a commercially confidential nature, in accordance with Article 119(1), point (e);

(f) inform the Agency of any actions foreseen or taken by that Member State to mitigate the shortage at national level.

3. Where the competent authority of the Member State has any information in addition to the information to be provided pursuant to this Article, it shall immediately provide such information to the Agency through the working party referred to in paragraph 1, point (c).

4. Following the addition of a medicinal product on the list of critical shortages of medicinal products referred to in Article 123(1), the competent authority of the Member State shall, through the working party referred to in paragraph 1, point (c), provide any information requested pursuant to Article 124(2), point (a), to the Agency.

5. Following any MSSG recommendations provided in accordance with Article 123(4), the competent authority of the Member State shall, through the working party referred to in paragraph 1, point (c):

(a) report to the Agency on any information received from the marketing authorisation holder as defined in Article 116(1) of the medicinal product concerned or from other actors pursuant to Article 120(2);

(b) comply and coordinate with any measures taken by the Commission pursuant to Article 126(1), point (a);

(c) take into account any MSSG recommendations referred to in Article 123(4);

(d) inform the Agency of any actions foreseen or taken by that Member State in accordance with points (b) and (c) and report on any other actions taken to mitigate or resolve the critical shortage in the Member State, as well as the results of these actions.

6. The Member States may request that the MSSG provide further recommendations, referred to in Article 123(4).

Article 122

Role of the Agency concerning shortages

1. For the purposes of Article 118(1), the Agency may request additional information from the competent authority of the Member State, through the working party

referred to in Article 121(1), point (c). The Agency may set a deadline for the submission of the information requested.

2. On the basis of Article 118(1), the Agency, in collaboration with the working party referred to in Article 121(1), point (c), shall identify the medicinal products for which the shortage cannot be resolved without EU coordination.

3. The Agency shall inform the MSSG of the shortages of the medicinal products that have been identified pursuant to paragraph 2.

4. For the purposes of fulfilling the tasks referred to in Articles 118(1), 123 and 124, the Agency shall ensure the following, in consultation with the working party referred to in Article 121(1), point (c):

   (a) set the criteria to adopt and review the list of critical shortages referred to in Article 123(1);

   (b) specify the tools, including the European Shortages Monitoring Platform ('ESMP'), established by Regulation (EU) 2022/123, once the scope is expanded pursuant to paragraph 6, the methods of and criteria for the monitoring and reporting provided for in Articles 119(1), point (a), and 121(2), point (a);

   (c) draw up guidance to allow marketing authorisation holders as defined in Article 116(1) to put in place the risk assessment of impact of suspension, cessation or withdrawal and the shortage mitigation plan as referred to in Article 118(2);

   (d) specify the methods for the provision of recommendations referred to in Article 123(4);

   (e) publish information covered by points (a) to (d) on a dedicated webpage on its web-portal referred to in Article 104.

5. For the duration of the critical shortage and until the MSSG considers it to be resolved, the Agency shall regularly report on the results of the monitoring referred to in Article 124 to the Commission and the MSSG, and in particular, it shall report any event that is likely to lead to a major event, as defined in Article 2 of Regulation (EU) 2022/123. Where a public health emergency is recognised in accordance with Regulation (EU) 2022/2371 or an event is recognised as a major event, in accordance with Regulation (EU) 2022/123, that Regulation applies.

6. For the purposes of implementing this Regulation, the Agency shall expand the scope of the ESMP. The Agency shall ensure that, where relevant, data is interoperable between the ESMP, Member States' IT systems and other relevant IT systems and databases, without duplication of reporting.

Article 123

Role of the MSSG and the list of critical shortages of medicinal products

1. Based on the monitoring referred to in Article 118(1), and following consultation with the Agency and the working party referred to in Article 121(1), point (c), the MSSG shall adopt a list of critical shortages of medicinal products authorised to be placed on the market of a Member State pursuant to Article 5 of [revised Directive 2001/83/EC]and for which co-ordinated Union level action is necessary ('the list of critical shortages of medicinal products').

2. The MSSG shall review the status of the critical shortage whenever necessary and shall update the list when it considers that a medicinal product needs to be added or that the critical shortage has been resolved based on the report pursuant to Article 122(5).

3. In addition, the MSSG shall amend its rules of procedure, and the rules of procedure of the working party referred to in Article 121(1), point (c), in accordance with the roles set out in this Regulation.

4. The MSSG may provide recommendations on measures to resolve or to mitigate the critical shortage, in accordance with the methods referred to in Article 122(4), point (d), to relevant marketing authorisation holders, the Member States, the Commission, the representatives of healthcare professionals or other entities.

Article 124

Management of the critical shortage

1. Following the addition of a medicinal product to the list of critical shortages pursuant to Article 123, paragraphs 1 and 2, and based on the continuous monitoring carried out in accordance with Article 118(1), the Agency, in coordination with the competent authority of the Member State, shall continuously monitor the critical shortage of that medicinal product.

2. For the purposes of paragraph 1, where that information is not already available to the Agency, the Agency may request relevant information on that critical shortage from:

   (a) the competent authority of the Member State concerned through the working party referred to in Article 121(1), point (c);

   (b) the marketing authorisation holder as defined in Article 116(1);

   (c) the other actors listed in Article 120(2).

   For the purposes of this paragraph, the Agency may set a deadline for the submission of the information requested.

3. The Agency shall establish within its web-portal referred to in Article 104 a publicly available webpage that provides information on actual critical shortages of medicinal products in cases in which the Agency has assessed the shortage and has provided recommendations to healthcare professionals and patients. This webpage shall also provide references to the lists of actual shortages published by the competent authorities of the Member State pursuant to Article 121(1), point (b).

Article 125

Obligations on the marketing authorisation holder in case of a critical shortage

1. Following the addition of a medicinal product to the list of critical shortages of medicinal products in accordance with Article 123, paragraphs 1 and 2, or recommendations provided in accordance with Article 123(4), the marketing authorisation holder as defined in Article 116(1) and subject to those recommendations shall:

   (a) provide any additional information that the Agency may request;

   (b) provide additional relevant information to the Agency;

(c) take into account the recommendations referred to in Article 123(4);

(d) comply with any measures taken by the Commission pursuant to Article 126(1), point (a), or actions taken by the Member State pursuant to Article 121(5), point (d);

(e) inform the Agency of any measures taken pursuant to points (c) and (d) and the report on results of such measures;

(f) inform the Agency of the end date of the critical shortage.

Article 126

Role of the Commission

1. The Commission shall, where it considers it appropriate and necessary:

(a) take into account the MSSG recommendations and implement relevant measures;

(b) inform the MSSG of those measures taken by the Commission.

2. The Commission may request the MSSG to provide recommendations referred to in Article 123(4).

SECTION 2

SECURITY OF SUPPLY

Article 127

Identification and management of critical medicinal products by the competent authority of the Member State

1. The competent authority of the Member State shall identify critical medicinal products in that Member State, using the methodology set out in Article 130(1), point (a).

2. The competent authority of the Member State acting through the working party referred to in Article 121(1), point (c), shall report to the Agency the critical medicinal products in that Member State identified pursuant to the paragraph 1, as well as the information received from the marketing authorisation holder as defined in Article 116(1).

3. For the purposes of the identification of critical medicinal products referred to in paragraph 1, the competent authority of the Member State may request relevant information including the shortage prevention plan referred to in Article 117 from the marketing authorisation holder as defined in Article 116(1).

4. For the purposes of the identification of critical medicinal products referred to in paragraph 1, the competent authority of the Member State may request relevant information from other entities including other marketing authorisation holders, importers and manufacturers of medicinal products or active substances and relevant suppliers of these, wholesale distributors, stakeholder representative associations or other persons or legal entities that are authorised or entitled to supply medicinal products to the public.

5. The competent authority of the Member State shall assess the merits of each confidentiality claim made by the marketing authorisation holder pursuant to Article 128(1), point (e), and shall protect any information that is commercially confidential against unjustified disclosure.

6. For the purposes of the adoption of the Union list of critical medicinal products pursuant to Article 131, each Member State shall, through the competent authority of the Member State concerned:

   (a) submit to the Agency the information referred to in Article 130(2), point (a), using the tools, methods of and criteria for the monitoring and reporting established pursuant to Article 130(1), point (c), by the deadline set by the Agency;

   (b) provide any relevant information to the Agency, including information on measures that have been taken by the Member State to strengthen the supply of that medicinal product;

   (c) provide updates to the information provided in accordance with points (a) and (b) to the Agency where necessary;

   (d) justify any failure to provide any of the requested information;

   (e) indicate the existence of any commercially confidential information reported as such by the marketing authorisation holder pursuant to Article 128(1), point (e), and provide the marketing authorisation holder's explanation of why that information is of a commercially confidential nature.

   Where necessary, the competent authority of the Member State may request an extension of the deadline set by the Agency to comply with the request for information in accordance with point (a) of the first subparagraph.

7. Following the addition of a medicinal product to the Union list of critical medicinal products in accordance with Article 131 or any recommendations provided in accordance with Article 132(1), the Member States shall:

   (a) provide any additional information that the Agency may request;

   (b) provide additional relevant information to the Agency;

   (c) comply and coordinate with any measures taken by the Commission pursuant to Article 134(1), point (a);

   (d) take into account any MSSG recommendations referred to in Article 132(1);

   (e) inform the Agency of any actions foreseen or taken in accordance with point (c) and (d) by that Member State, as well as the results of these actions.

8. Member States that take an alternative course of action in respect of paragraph 7, points (c) and (d), shall share the reasons for doing so with the Agency in a timely manner.

Article 128

Obligations of the marketing authorisation holder with regard to critical medicinal products

1. For the purposes of Article 127, paragraphs 1 and 3, and Article 131(1), the marketing authorisation holder as defined in Article 116(1) shall:

(a) submit the information requested in accordance with Articles 127(3), 130(2), point (b), and 130(4), point (b), to the competent authority concerned as defined in Article 116(1), without undue delay, using the tools, methods of and criteria for the monitoring and reporting established pursuant to Article 130(1), point (c), by the deadline set by that competent authority concerned;

(b) provide updates to the information provided in accordance with point (a) where necessary;

(c) justify any failure to provide any of the requested information;

(d) where necessary, submit a request to the competent authority concerned as defined in Article 116(1) for an extension of the deadline set by that competent authority in accordance with point (a), and

(e) indicate whether the information provided in accordance with point (a) contain any commercially confidential information, identify the relevant parts of that information having a commercially confidential nature and explain why that information is of such nature.

2. The marketing authorisation as defined in Article 116(1) authorisation shall be responsible for providing correct, not misleading, and complete information as requested by the competent authority concerned as defined in Article 116(1) and shall have the duty to cooperate and to disclose on their own motion any relevant information without undue delay to that competent authority and to update the information as soon as that information becomes available.

Article 129

Obligations on other actors

For the purposes of Article 127(4) and Article 130(2), point (c), and Article 130(4), point (c), where relevant, upon request from the competent authority concerned as defined in Article 116(1), entities including other marketing authorisation holders as defined in Article 116(1), importers and manufacturers of medicinal products or active substances and relevant suppliers of these, wholesale distributors, stakeholder representative associations or other persons or legal entities that are authorised or entitled to supply medicinal products to the public shall provide any information requested in a timely manner.

Article 130

Role of the Agency

1. The Agency shall, in collaboration with the working party referred to in Article 121(1), point (c), ensure the following:

(a) develop a common methodology to identify critical medicinal products, including the evaluation of vulnerabilities with respect to the supply chain of those medicines, in consultation, where appropriate, with relevant stakeholders;

(b) specify the procedures and criteria for establishing and reviewing the Union list of critical medicinal products referred to in Article 131;

(c) specify the tools, methods of and criteria for the monitoring and reporting provided for in Articles 127(6), point (a), and 128(1), point (a);

(d) specify the methods for the provision and review of MSSG recommendations referred to in Article 132, paragraphs 1 and 3.

The Agency shall publish the information referred to in points (b), (c) and (d) on a dedicated webpage on its web-portal.

2. Following the reports and information provided by the Member States and marketing authorisation holders in accordance with Article 127, paragraphs 2 and 6, and Article 128(1), the Agency, may request the relevant information from:

(a) the competent authority of the Member State concerned;

(b) the marketing authorisation holder of the medicinal product, including the shortage prevention plan, referred to in Article 117;

(c) other entities including other marketing authorisation holders, importers and manufacturers of medicinal products or active substances and relevant suppliers of these, wholesale distributors, stakeholder representative associations or other persons or legal entities that are authorised or entitled to supply medicinal products to the public.

The Agency, in consultation with the working party referred to in Article 121(1), point (c), shall report the information referred to in Article 127, paragraphs 2 and 6, and Article 128(1) to the MSSG.

3. For the purposes of Article 127(6), point (e), and Article 128(1), point (e), the Agency shall assess the merits of each confidentiality claim and protect commercially confidential information against unjustified disclosure.

4. Following the adoption of the Union list of critical medicinal products in accordance with Article 131, the Agency may request additional information from:

(a) the competent authority of the Member State concerned;

(b) the marketing authorisation holder as defined in Article 116(1);

(c) other entities including other marketing authorisation holders, importers and manufacturers of medicinal products or active substances and relevant suppliers of these, wholesale distributors, stakeholder representative associations or other persons or legal entities that are authorised or entitled to supply medicinal products to the public.

5. Following the adoption of the Union list of critical medicinal products in accordance with Article 131, the Agency shall report to the MSSG on any relevant information received from the marketing authorisation holder pursuant to Article 133 and the competent authority of the Member State in accordance with Article 127, paragraphs 7 and 8.

6. The Agency shall make publicly available via the web-portal referred to in Article 104 the MSSG recommendations referred to in Article 132(1).

Article 131

The Union List of Critical Medicinal Products

1. Following the reporting referred to in Article 130, paragraph 2, second subparagraph, and Article 130(5), the MSSG shall consult the working party referred to in Article 121(1), point (c). Based on this consultation, the MSSG shall propose a Union list of critical medicinal products authorised to be placed on the market of a Member State

pursuant to Article 5 of [revised Directive 2001/83/EC] and for which coordinated Union level action is necessary ("the Union list of critical medicinal products").

2. The MSSG may propose updates to the Union list of critical medicines to the Commission, where necessary.

3. The Commission, taking into account the proposal of the MSSG, shall adopt and update the Union list of critical medicinal products by means of an implementing act and communicate the adoption of the list and any updates to the Agency and the MSSG. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 173(2).

4. Following the adoption of the Union list of critical medicinal products in accordance with paragraph 3, the Agency shall immediately publish this list and any updates to this list on its web-portal referred to in Article 104.

Article 132

Role of the MSSG

1. Following the adoption of the Union list of critical medicinal products pursuant to Article 131(3), in consultation with the Agency and the working party referred to in Article 121(1), point (c), the MSSG may provide recommendations, in accordance with the methods referred to in Article 130(1), point (d), on appropriate security of supply measures to marketing authorisation holders as defined in Article 116(1), the Member States, the Commission or other entities. Such measures may include recommendations on diversification of suppliers and inventory management.

2. The MSSG shall amend its rules of procedure, and the rules of procedure of the working party referred to in Article 121(1), point (c), in accordance with the tasks set out in this section.

3. Following the report pursuant to Article 130(5), the MSSG shall review its recommendations in accordance with the methods referred to in Article 130(1), point (d).

4. The MSSG may request the Agency to request further information from the Member States or marketing authorisation holder of the medicinal product as defined in Article 116(1) and included on the Union list of critical medicinal products or other relevant entities referred to in Article 129.

Article 133

Obligations on the marketing authorisation holder after the MSSG recommendations

Following the addition of a medicinal product to the Union list of critical medicinal products in accordance with Article 131(3) or any recommendations provided in accordance with Article 132(1), the marketing authorisation holder as defined in Article 116(1) of a medicinal product on that list or subject to those recommendations shall:

(a) provide any additional information that the Agency may request;

(b) provide additional relevant information to the Agency;

(c) take into account the recommendations referred to in Article 132(1);

(d) comply with any measures taken by the Commission in accordance with Article 134(1), point (a), or by the Member State pursuant to Article 127(7), point (e);

(e) inform the Agency of any measures taken and report on the results of such measures.

Article 134

Role of the Commission

1. The Commission may, where it considers it appropriate and necessary:

   (a) take into account the MSSG recommendations and implement the relevant measures;

   (b) inform the MSSG of those measures taken by the Commission.

   (c) request the MSSG to provide information or an opinion or further recommendations referred to in Article 132(1).

2. The Commission, taking into consideration the information or the opinion, referred to in paragraph 1, or MSSG recommendations, may decide to adopt an implementing act to improve security of supply. The implementing act may impose contingency stock requirements of active pharmaceutical ingredient or finished dosage forms, or other relevant measures required to improve security of supply, on marketing authorisation holders, wholesale distributors or other relevant entities.

3. The implementing act referred to in paragraph 2 shall be adopted in accordance with the examination procedure referred to in Article 173(2).

CHAPTER XI
EUROPEAN MEDICINES AGENCY

SECTION 1

TASKS OF THE AGENCY

Article 135

Establishment

The functioning of the European Medicines Agency established by Regulation (EC) No 726/2004 (the 'Agency') shall continue in accordance with the present Regulation.

The Agency shall be responsible for coordinating the existing scientific resources put at its disposal by Member States for the evaluation, supervision and pharmacovigilance of medicinal products for human use and of veterinary medicinal products.

Article 136

Legal status

1. The Agency shall have legal personality.

2. In each of the Member States, the Agency shall enjoy the most extensive legal capacity accorded to legal persons under their laws. It may, in particular, acquire or dispose of movable and immovable property, and be party to legal proceedings.

3. The Agency shall be represented by an Executive Director.

Article 137

Seat

The seat of the Agency shall be established in Amsterdam, the Netherlands.

Article 138

Objectives and tasks of the Agency

1. The Agency shall provide the Member States and the institutions of the Union with the best possible scientific opinion on any question relating to the evaluation of the quality, safety and efficacy of medicinal products for human use, veterinary medicinal products, which is referred to it in accordance with the Union legal acts relating to medicinal products for human use or veterinary medicinal products.

   The Agency, acting particularly through its Committees, shall carry out the following tasks:

   (a) coordinating the scientific evaluation of the quality, safety and efficacy of medicinal products for human use, which are subject to Union marketing authorisation procedures;

   (b) coordinating the scientific evaluation of the quality, safety and efficacy of veterinary medicinal products, which are subject to Union marketing authorisation procedures in accordance with Regulation (EU) 2019/6 and the performance of other tasks set out in Regulation (EU) 2019/6 and Regulation (EC) 470/2009;

   (c) transmitting on request and making publicly available assessment reports, summaries of product characteristics, labels and package leaflets for the medicinal products for human use;

   (d) coordinating the monitoring of medicinal products for human use which have been authorised in the Union and providing advice on the measures necessary to ensure the safe and effective use of those products, in particular by coordinating the evaluation and implementation of pharmacovigilance obligations and systems and the monitoring of such implementation;

   (e) ensuring the collation and dissemination of information on suspected adverse reactions to medicinal products for human use authorised in the Union by means of databases that are permanently accessible to all Member States;

   (f) assisting Member States with the rapid communication of information on pharmacovigilance concerns relating to medicinal products for human use to healthcare professionals and coordinating the safety announcements of the competent authorities of the Member States;

   (g) distributing appropriate information on pharmacovigilance concerns relating to medicinal products for human use to the general public, in particular by setting up and maintaining a European medicines web-portal;

   (h) coordinating, as regards medicinal products for human use and veterinary medicinal products, the verification of compliance with the principles of good manufacturing practice, good laboratory practice, good clinical practice, good pharmacovigilance practice and, as regards medicinal products for human use, the verification of compliance with pharmacovigilance obligations;

(i) ensuring the secretariat of the Joint Audit Programme referred to in Article 54;

(j) upon request, providing technical and scientific support in order to improve cooperation between the Union, its Member States, international organisations and third countries on scientific and technical issues relating to the evaluation and monitoring of medicinal products for human use and of veterinary medicinal products, in particular in the framework of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and the Veterinary International Conference on Harmonization;

(k) coordinating as referred to in Article 53 a structured cooperation on inspections in third countries between Member States, the European Directorate for the Quality of Medicines and Healthcare of the Council of Europe, the World Health Organization or trusted international authorities, by means of international inspection programmes;

(l) conducting inspections with Member States to verify the compliance with the principles of good manufacturing practice, including issuing GMP certificates and good clinical practice at the request of the Supervisory Authority referred to in Article 50(2) whenever additional capacity is needed to carry out inspection of Union interest including in response of public health emergencies;

(m) recording the status of marketing authorisations for medicinal products for human use granted in accordance with Union marketing authorisation procedures;

(n) creating a database on medicinal products for human use, to be accessible to the general public, and ensuring that it is updated, and managed independently of pharmaceutical companies; the database is to facilitate the search for information already authorised for package leaflets; it is to include a section on medicinal products for human use authorised for the treatment of children; the information provided to the general public is to be worded in an appropriate and comprehensible manner;

(o) assisting the Union and its Member States in the provision of information to health-care professionals and the general public about medicinal products for human use and about veterinary medicinal products evaluated by the Agency;

(p) providing scientific advice to undertakings or, as relevant, not-for-profit entities on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of medicinal products for human use;

(q) supporting, through enhanced scientific and regulatory advice, the development of medicinal products which are of major interest from the point of view of public health, including antimicrobial resistance, and in particular from the viewpoint of therapeutic innovation (priority medicines);

(r) checking that the conditions laid down in Union legal acts on medicinal products for human use and on veterinary medicinal products and in the marketing authorisations are met in the case of parallel distribution of medicinal products for human use and on veterinary medicinal products authorised in accordance with this Regulation or, as applicable, Regulation (EU) 2019/6;

(s) drawing up, at the Commission's request, any other scientific opinion concerning the evaluation of medicinal products for human use and of veterinary medicinal products or the starting materials used in the manufacture of medicinal products for human use;

(t) with a view to the protection of public health, compiling scientific information concerning pathogenic agents which might be used in biological warfare, including the existence of vaccines and other medicinal products for human use and other veterinary medicinal products available to prevent or treat the effects of such agents;

(u) coordinating the supervision of the quality of medicinal products for human use and of veterinary medicinal products placed on the market by requesting testing of compliance with their authorised specifications to the European Directorate for the Quality of Medicines and Healthcare that coordinates with the Official Medicines Control Laboratory or by a laboratory that a Member State has designated for that purpose. The Agency and the European Directorate for the Quality of Medicines and Healthcare shall enter into a written contract for the provision of services to the Agency under this subparagraph;

(v) forwarding annually to the budgetary authority aggregated information on procedures for medicinal products for human use and veterinary medicinal products;

(w) taking decisions as referred to in Article 6(5) of [revised Directive 2001/83/EC];

(x) contributing to the joint reporting with the European Food Safety Authority and European Centre for Disease Prevention and Control on the sales and use of antimicrobials in human and veterinary medicine as well as on the situation as regards antimicrobial resistance in the Union based on contributions received by Member States, taking into account the reporting requirements and periodicity in Article 57 of Regulation (EU) 2019/6. Such joint reporting shall be carried out at least every three years;

(y) adopting a decision granting, refusing or transferring an orphan designation;

(z) adopting decisions on paediatric investigation plans, waivers and deferrals in relation to medicinal products;

(za) providing regulatory support and scientific advice for the development of orphan and paediatric medicinal products;

(zb) coordinating assessment of and certifying quality master files for medicinal products for human use as well as, where necessary, coordinating inspections of manufacturers applying for or holding a certificate for a quality master file;

(zc) establishing a mechanism of consultation of authorities or bodies active along the life cycle of medicinal products for human use for exchange of information and pooling of knowledge on general issues of scientific or technical nature related to the tasks of the Agency;

(zd) developing coherent scientific assessment methodologies in the fields falling within its mission;

(ze) cooperating with EU decentralised agencies and other scientific authorities and bodies established under Union law, notably the European Chemicals Agency, the European Food Safety Authority, the European Centre for Disease Prevention and Control and the European Environment Agency as regards the scientific assessment of relevant substances, exchange of data and information and development of coherent scientific methodologies, including replacing, reducing or refining animal testing, taking into account the specificities of the assessment of medicinal products;

(zf) coordinating the monitoring and management of critical shortages of medicinal products included in the list referred to in Article 123(1);

(zg) coordinating the identification and management of the Union list of critical medicinal products referred to in Article 131;

(zh) supporting the working party referred to in Article 121(1), point (c), and the MSSG in their tasks in relation to critical shortages and critical medicines;

(zi) providing regulatory support and scientific advice for, and facilitate the development, validation and regulatory uptake of new-approach methodologies that replace the use of animals in testing;

(zj) facilitating joint non-clinical studies between applicants and holders to avoid unnecessary duplication of tests using live animals;

(zk) facilitating data sharing of results from non-clinical studies on live animals;

(zl) drawing up scientific guidelines to facilitate the implementation of the definitions established in this Regulation and in [revised Directive 2001/83], and for the environmental risk assessment of medicinal products for human use, in consultation with the Commission and the Member States.

2. The database provided for in paragraph 1, point (n), shall include all medicinal products for human use authorised in the Union together with the summaries of product characteristics, the package leaflet and the information shown on the labelling. Where relevant, it shall include the electronic links to the dedicated webpages where the marketing authorisation holders have reported the information pursuant to Article 40(4), point (b), and Article 57 of [revised Directive 2001/83/EC].

For the purposes of the database, the Agency shall set up and maintain a list of all medicinal products for human use authorised in the Union. To this effect:

(a) the Agency shall make public a format for the electronic submission of information on medicinal products for human use;

(b) marketing authorisation holders shall electronically submit to the Agency information on all medicinal products for human use authorised in the Union and shall inform the Agency of any new or varied marketing authorisations granted in the Union, using the format referred to in point (a).

Where appropriate, the database shall also include references to clinical trials currently being carried out or already completed, contained in the clinical trials database provided for in Article 81 of Regulation (EU) No 536/2014.

Article 139

Coherence of scientific opinions with other Union bodies

1. The Agency shall take the necessary and appropriate measures to monitor and identify at an early stage any potential source of divergence between its scientific opinions and the scientific opinions issued by other Union bodies and agencies carrying out similar tasks in relation to issues of common concern.

2. Where the Agency identifies a potential source of divergence, it shall contact the body or agency in question to ensure that all relevant scientific or technical information is shared and in order to identify potentially contentious scientific or technical issues.

3. Where a substantive divergence over scientific or technical issues is identified and the body concerned is a Union Agency or a scientific committee, the Agency and the body concerned shall cooperate to resolve the divergence, and inform the Commission without undue delay.

4. The Commission may ask the Agency to conduct an assessment as regards specifically the use of the substance concerned in medicinal products. The Agency shall make public its assessment stating clearly the reasons for its specific scientific conclusions.

5. To enable coherence between scientific opinions and to avoid duplication of tests, the Agency shall make arrangements with other bodies or agencies established under Union law for cooperation on scientific assessments and methodologies. The Agency shall also make arrangements for the exchange of data and information on relevant substances with the Commission, Member States' authorities and other Union Agencies, in particular for environmental risk assessments, non-clinical studies and maximum residue limits.

   These arrangements shall seek to ensure that exchanges of data and information are made available in electronic formats and shall protect the commercially confidential nature of the information exchanged and be without prejudice to the provisions on regulatory protection.

Article 140

Scientific opinions in the context of international collaboration

1. The Agency may give a scientific opinion, in particular in the context of cooperation with the World Health Organization, for the evaluation of certain medicinal products for human use intended for markets outside the Union. For this purpose, an application shall be submitted to the Agency in accordance with the provisions of Article 6. Such application may be submitted and assessed together with a marketing authorisation application or any subsequent variation for the EU. The Agency may, after consulting the World Health Organization, and as appropriate other relevant organisations, draw up a scientific opinion in accordance with Articles 6, 10 and 12. The provisions of Article 13 shall not apply.

2. The Agency shall establish specific procedural rules for the implementation of paragraph 1, as well as for the provision of scientific advice.

Article 141

International regulatory cooperation

1. In so far as is necessary in order to achieve the objectives set out in this Regulation, and without prejudice to the respective competences of the Member States and the

institutions of the Union, the Agency may cooperate with the competent authorities of third countries and/or with international organisations.

To this end, the Agency may, subject to prior approval by the Commission, establish working arrangements with the authorities of third countries and international organisations, with regard to:

(a) the exchange of information, including non-public information, where relevant jointly with the Commission;

(b) sharing of scientific resources and expertise, with a view to facilitating collaboration, while maintaining independent assessment in full compliance with the provisions of this Regulation and [revised Directive 2001/83/EC] and under conditions determined beforehand by the Management Board, in agreement with the Commission;

(c) the participation in certain aspects of the Agency's work, under conditions determined beforehand by the Management Board, in agreement with the Commission.

These arrangements shall not create legal obligations incumbent on the Union and its Member States.

2. The Agency shall ensure that it is not seen as representing the Union position to an outside audience or as committing the Union to international cooperation.

3. The Commission may, in agreement with the Management Board and the relevant committee, invite representatives of international organisations with an interest in the harmonisation of technical requirements applicable to medicinal products for human use and to veterinary medicinal products to participate as observers in the work of the Agency. The conditions for participation shall be determined in advance by the Commission.

SECTION 2

STRUCTURE AND OPERATION

Article 142

Administrative and management structure

The Agency shall comprise:

(a) a Management Board, which shall exercise the functions set out in Articles 143, 144 and 154.

(b) an Executive Director, who shall exercise the responsibilities set out in Article 145;

(c) a Deputy Executive Director who shall exercise the responsibilities set out in Article 145(7);

(d) the Committee for Medicinal Products for Human Use;

(e) the Pharmacovigilance Risk Assessment Committee;

(f) the Committee for Veterinary Medicinal Products set up pursuant to Article 139(1) of Regulation (EU) 2019/6;

(g) the Herbal Medicinal Products working group set up pursuant to Article 141 of [revised Directive 2001/83/EC];

(h) the Emergency task force set up pursuant to Article 15 of Regulation (EU) 2022/123;

(i) the MSSG set up pursuant to Article 3 of Regulation (EU) 2022/123;

(j) the Medical Device Shortages Steering Group, set up pursuant to Article 21 of Regulation (EU) 2022/123;

(k) the inspection working group;

(l) a Secretariat, which shall provide technical, scientific and administrative support to all bodies of the Agency and ensure appropriate coordination between them, and which shall provide technical and administrative support for the coordination group referred to in Article 37 of [revised Directive 2001/83/EC] and ensure appropriate coordination between it and the Committees. It shall also undertake the work required of the Agency under the procedures for the assessment and preparations of decisions for paediatric investigation plans, waivers, deferrals or orphan designations.

Article 143

Management Board

1. The Management Board shall be composed of one representative from each Member State, two representatives of the Commission and two representatives of the European Parliament, all with voting rights.

   In addition, two representatives of patients' organisations, one representative of doctors' organisations and one representative of veterinarians' organisations, all with voting rights, shall be appointed by the Council in consultation with the European Parliament on the basis of a list drawn up by the Commission which includes appreciably more names than there are posts to be filled. The list drawn up by the Commission shall be forwarded to the European Parliament, together with the relevant background documents. As quickly as possible, and at the latest within three months of notification, the European Parliament may submit its views for consideration to the Council, which shall then appoint these representatives to the Management Board.

   The members of the Management Board shall be appointed in such a way as to guarantee the highest levels of specialist qualifications, a broad spectrum of relevant expertise and the broadest possible geographic spread within the European Union.

2. Members of the Management Board and their alternates shall be appointed on the basis of their knowledge, recognised experience and commitment in the field of medicinal products for human or veterinary use, taking into account relevant managerial, administrative and budgetary expertise [which are to be used to further the objectives of this Regulation].

   All parties represented in the Management Board shall make efforts to limit turnover of their representatives, in order to ensure continuity of the work of the Management Board. All parties shall aim to achieve a balanced representation between men and women on the Management Board.

3. Each Member State and the Commission shall appoint their members of the Management Board as well as an alternate who will replace the member in their absence and vote on their behalf.

4. The term of office for members and their alternates shall be four years. That term shall be extendable.

5. The Management Board shall elect a chairperson and a Deputy chairperson from among its members.

   The chairperson and the Deputy chairperson shall be elected by a majority of two-thirds of the members of the Management Board with voting rights.

   The Deputy chairperson shall automatically replace the chairperson if they are prevented from attending to their duties.

   The term of office of the chairperson and the deputy chairperson shall be four years. The term of office may be renewed once. If however, their membership of the Management Board ends at any time during their term of office, their term of office shall automatically expire on that date.

6. Without prejudice to paragraph 5 and Article 144, points (e) and (g), the Management Board shall take decisions by absolute majority of its members with voting rights.

7. The Management Board shall adopt its rules of procedure.

8. The Management Board may invite the chairpersons of the scientific committees to attend its meetings, but they shall not have the right to vote.

9. The Management Board may invite any person whose opinion may be of interest to attend its meetings as an observer.

10. The Management Board shall approve the annual work programme of the Agency programme and forward it to the European Parliament, the Council, the Commission and the Member States.

11. The Management Board shall adopt the annual report on the Agency's activities and forward it by 15 June at the latest to the European Parliament, the Council, the Commission, the European Economic and Social Committee, the Court of Auditors and the Member States.

Article 144

Tasks of the Management Board

The Management Board shall:

(a) give the general orientations for the Agency's activities;

(b) adopt an opinion on the rules of procedures of the Committee for Medicinal Products for Human Use (Article 148) and the Committee for Veterinary Medicinal Products (Article 139 of Regulation (EU) 2019/6);

(c) adopt procedures for the performance of scientific services regarding medicinal products for human use (Article 152);

(d) appoint the Executive Director, and where relevant extend their term of office or remove them from office, in accordance with Article 145;

(e) adopt yearly the Agency's draft single programming document before its submission to the Commission for its opinion, and the Agency's single programming document by a majority of two-thirds of members entitled to vote and in accordance with Article 154;

(f) assess and adopt a consolidated annual activity report on the Agency's activities and send it by 1 July each year to the European Parliament, the Council, the Commission and the Court of Auditors. The consolidated annual activity report shall be made public;

(g) adopt the annual budget of the Agency by a majority of two-thirds of the members entitled to vote and in accordance with Article 154;

(h) adopt the financial rules applicable to the Agency in accordance with Article 155;

(i) exercise, with respect to the staff of the Agency, the powers conferred by Regulation No 31 by the Council of the European Economic Community, and Regulation No 11 and by the Council of the European Atomic Energy Community ('Staff Regulations' and 'Conditions of Employment of Other Servants')[39] on the Appointing Authority and on the Authority Empowered to Conclude a Contract of Employment ('the appointing authority powers');

(j) adopt implementing rules for giving effect to the Staff Regulations and the Conditions of Employment of Other Servants in accordance with Article 110 of the Staff Regulations;

(k) develop contacts with stakeholders and stipulate the conditions applicable as mentioned in Article 163;

(l) adopt an anti-fraud strategy, proportionate to risks of fraud taking into account the costs and benefits of the measures to be implemented;

(m) ensure adequate follow-up to findings and recommendations stemming from the internal or external audit reports and evaluations, as well as from investigations of the European Anti-fraud Office ('OLAF') and the European Public Prosecutor's Office ('EPPO');

(n) adopt rules to ensure the availability to the public of information concerning the authorisation or supervision of medicinal products for human use as mentioned in Article 166;

(o) adopt an efficiency gains and synergies strategy;

(p) adopt a strategy for cooperation with third countries or international organisations;

(q) adopt a strategy for the organisational management and internal control systems.

The Management Board shall adopt, in accordance with Article 110 of the Staff Regulations, a decision based on Article 2(1) of the Staff Regulations and on Article 6 of the Conditions of Employment of Other Servants, delegating relevant appointing authority powers to the Executive Director and defining the conditions under which that delegation of powers can be suspended. The Executive Director shall be authorised to sub-delegate those powers.

[39] Regulation No 31 (EEC), 11 (EAEC) by the Council of the European Economic Community and by the Council of the European Atomic Energy Community, laying down the Staff Regulations of Officials and the Conditions of Employment of Other Servants of the European Economic Community and the European Atomic Energy Community (OJ 45, 14.6.1962, p. 1385).

Where exceptional circumstances so require, the Management Board may, by way of a decision, temporarily suspend the delegation of the appointing authority powers to the Executive Director and those sub-delegated by the latter and exercise them itself or delegate them to one of its members or to a staff member other than the Executive Director.

Article 145

Executive Director

1. The Executive Director shall be engaged as a temporary agent of the Agency under Article 2, point (a), of the Conditions of Employment of Other Servants.

2. The Executive Director shall be appointed by the Management Board from a list of candidates proposed by the Commission following an open and transparent selection procedure.

   For the purpose of concluding the contract with the Executive Director, the Agency shall be represented by the Chairperson of the Management Board.

   Before appointment, the candidate nominated by the Management Board shall be immediately invited to make a statement to the European Parliament and to answer any questions put by its Members.

3. The term of office of the Executive Director shall be five years. By the end of that period the Commission shall undertake an assessment that takes into account an evaluation of the Executive Director's performance and the Agency's future tasks and challenges.

4. The Management Board, acting on a proposal from the Commission that takes into account the assessment referred to in paragraph 3, may extend the term of office of the Executive Director once, for no more than five years.

   An Executive Director whose term of office has been extended may not participate in another selection procedure for the same post at the end of the overall period.

5. The Executive Director may be removed from office only upon a decision of the Management Board acting on a proposal from the Commission.

6. The Management Board shall reach decisions on appointment, extension of the term of office or removal from office of the Executive Director on the basis of a two-thirds majority of its members with voting rights.

7. The Executive Director will be assisted by a Deputy Executive Director. If the Executive Director is absent or indisposed, the Deputy Executive Director shall take their place.

8. The Executive Director shall manage the Agency. The Executive Director shall be accountable to the Management Board. Without prejudice to the powers of the Commission and of the Management Board, the Executive Director shall be independent in the performance of their duties and shall neither seek nor take instructions from any government or from any other body.

9. The Executive Director shall report to the European Parliament on the performance of their tasks when invited to do so. The Council may invite the Executive Director to report on the performance of those tasks.

10. The Executive Director shall be the legal representative of the Agency. The Executive Director shall be responsible for:

(a) the day-to-day administration of the Agency;

(b) implementing decisions adopted by the Management Board;

(c) managing all the Agency resources necessary for conducting the activities of the Committees referred to in Article 142, including making available appropriate scientific and technical support to those Committees, and for making available appropriate technical support to the coordination group;

(d) ensuring that the time-limits laid down in Union legal acts for the adoption of opinions by the Agency are complied with;

(e) ensuring appropriate coordination between the Committees referred to in Article 142 and, where necessary, between those Committees and the coordination group or other working groups of the Agency;

(f) the preparation of the draft statement of estimates of the Agency's revenue and expenditure, and execution of its budget;

(g) the preparation of the draft single programming document and the submission it to the Management Board after consulting the Commission;

(h) implementing the single programming document and report to the Management Board on its implementation;

(i) preparing the Agency’s consolidated annual activity report on the Agency's activities and presenting it to the Management Board for assessment and adoption;

(j) all staff matters;

(k) providing the secretariat for the Management Board;

(l) without prejudice to the competences of OLAF and EPPO, protecting the financial interests of the Union by applying preventive measures against fraud, corruption and any other illegal activities, by effective checks and, if irregularities are detected, by recovering amounts wrongly paid and, where appropriate, by imposing effective, proportionate and dissuasive administrative and financial penalties;

(m) reporting, on the basis of key performance indicators agreed by the Management board, on the IT infrastructure developed by the Agency by means of implementation of legislation, in term of timing, budgetary compliance and quality.

11. Each year the Executive Director shall submit a draft report covering the activities of the Agency in the previous year and a draft work programme for the coming year to the Management Board for approval, making a distinction between the Agency's activities concerning medicinal products for human use, those concerning herbal medicinal products and those concerning veterinary medicinal products.

The draft report covering the activities of the Agency in the previous year shall include information about the number of applications evaluated by the Agency, the time taken for completion of the evaluation, and the medicinal products for human use and veterinary medicinal products authorised, rejected or withdrawn.

Article 146

Scientific Committees – General provisions

1. The scientific committees shall be responsible for providing the scientific opinions or recommendations of the Agency, each within their own spheres of competence, and shall have the possibility, where necessary of organising public hearings.

2. The membership of the scientific committees shall be made public. When each appointment is published, the professional qualifications of each member shall be specified.

3. The Executive Director of the Agency or their representative and representatives of the Commission shall be entitled to attend all meetings of the scientific committees referred to in Article 142, working parties and scientific advisory groups and all other meetings convened by the Agency or its scientific committees.

4. Members of the scientific committees and experts responsible for evaluating medicinal products and nominated by Member States shall rely on the scientific evaluation and resources available to national competent authorities responsible for marketing authorisation, and on external experts proposed by Member States or selected by the Agency. Each competent national authority shall monitor the scientific level and independence of the evaluation carried out and facilitate the activities of nominated members of the Committees and experts. Member States shall refrain from giving those members and experts any instruction which is incompatible with their own individual tasks or with the tasks and responsibilities of the Agency.

5. The members of the scientific committees may be accompanied by experts in specific scientific or technical fields.

6. When preparing any opinion or recommendation, the scientific committees shall use their best endeavours to reach a scientific consensus. If such a consensus cannot be reached, the opinion shall consist of the position of the majority of members and divergent positions, with the grounds on which they are based.

7. The Committee for Medicinal Products for Human Use may, if they consider it appropriate, seek guidance on important questions of a general scientific or ethical nature.

8. The scientific committees and any working parties and scientific advisory groups established in accordance with this Article shall in general matters establish contacts, on an advisory basis, with parties concerned with the use of medicinal products for human use, in particular patient and consumer organisations and healthcare professionals' associations. For that purpose working groups of patient and consumer organisations and healthcare professionals' associations shall be established by the Agency. They shall ensure a fair representation of healthcare professionals, patients and consumers covering a wide range of experience and disease areas, including orphan, paediatric and geriatric diseases and advanced therapy medicinal products, and a broad geographical range.

   Rapporteurs appointed by the scientific committees may, on an advisory basis, establish contacts with representatives of patient organisations and healthcare professionals' associations relevant to the therapeutic indication of the medicinal product for human use.

9. The Committee for Veterinary Medicinal Products shall operate in accordance with Regulation (EU) No 2019/6 and paragraphs 1, 2 and 3.

Article 147

Conflict of interest

1. Members of the Management Board, members of the committees, rapporteurs and experts shall not have financial or other interests in the pharmaceutical industry which could affect their impartiality. They shall undertake to act in the public interest and in an independent manner, and shall make an annual declaration of their financial interests. All indirect interests which could relate to this industry shall be entered in a register held by the Agency which is accessible to the public, on request, at the Agency's offices.

   The Agency's code of conduct shall provide for the implementation of this Article with particular reference to the acceptance of gifts.

2. Members of the Management Board, members of the committees, rapporteurs and experts who participate in meetings or working groups of the Agency shall declare, at each meeting, any specific interests which could be considered to be prejudicial to their independence with respect to the items on the agenda. These declarations shall be made available to the public.

Article 148

Committee for Medicinal Products for Human Use activities

1. The Committee for Medicinal Products for Human Use shall be responsible for drawing up the opinion of the Agency on any matter concerning the admissibility of the files submitted in accordance with the centralised procedure, the granting, variation, suspension or revocation of an authorisation to place a medicinal product for human use on the market in accordance with the provisions of this Chapter, and pharmacovigilance. For the fulfilment of its pharmacovigilance tasks, including the approval of risk management systems and monitoring their effectiveness provided for under this Regulation, the Committee for Medicinal Products for Human Use shall rely on the scientific assessment and recommendations of the Pharmacovigilance Risk Assessment Committee referred to in Article 142, point (e).

2. In addition to their task of providing objective scientific opinions to the Union and Member States on the questions which are referred to them, the members of the Committee for Medicinal Products for Human Use shall ensure that there is appropriate coordination between the tasks of the Agency and the work of competent national authorities, including the consultative bodies concerned with the marketing authorisation.

3. The Committee for Medicinal Products for Human Use shall be composed of the following:

   (a) one member and one alternate member appointed by each Member State, in accordance with paragraph 6;

   (b) four members and one alternate members appointed by the Commission, on the basis of a public call for expressions of interest, after consulting the European Parliament, in order to represent healthcare professionals;

   (c) four members and four alternate members appointed by the Commission, on the basis of a public call for expressions of interest, after consulting the European Parliament, in order to represent patient organisations.

4. The Committee for Medicinal Products for Human Use may co-opt a maximum of five additional members chosen on the basis of their specific scientific competence. Those members shall be appointed for a term of three years, which may be renewed, and shall not have alternates.

With a view to the co-opting of such members, the Committee for Medicinal Products for Human Use shall identify the specific complementary scientific competence of the additional member or members. Co-opted members shall be chosen among experts nominated by Member States or the Agency.

5. The alternates shall represent and vote for the members in their absence and may also be appointed to act as rapporteurs in accordance with Article 152.

Members and alternates shall be chosen for their role and experience in the evaluation of medicinal products for human use as appropriate and shall represent the competent authorities of the Member States.

6. The members and alternate members of the Committee for Medicinal Products for Human Use shall be appointed on the basis of their relevant expertise in the assessment of medicinal products which should cover all types of medicinal products covered by [revised Directive 2001/83/EC] and this Regulation and which include medicinal products for rare and paediatric diseases, advance therapy medicinal products, biological and biotechnological products, in order to guarantee the highest levels of specialist qualifications and a broad spectrum of relevant expertise. The Member States shall cooperate in order to ensure that the final composition of the Committee for Medicinal Products for Human Use provides appropriate and balanced coverage of all scientific areas relevant to its tasks taking into account scientific developments and new types of medicinal products. For this purpose, Member States shall liaise with the Management Board and the Commission.

7. The members and alternate members of the Committee for Medicinal Products for Human Use shall be appointed for a term of thee years, which may be renewed following the procedures referred to in paragraph 6. The Committee shall elect its chairperson and vice-chairperson from among its members for a term of 3 years, which may be prolonged once.

8. The Committee for Medicinal Products for Human Use shall establish its own rules of procedure.

These rules shall, in particular, lay down:

(a) procedures for appointing and replacing the chairperson;

(b) procedures relating to working parties and scientific advisory groups; and

(c) a procedure for the urgent adoption of opinions, particularly in relation to the provisions of this Regulation on market surveillance and pharmacovigilance.

They shall enter into force after receiving a favourable opinion from the Commission and the Management Board.

Article 149

Pharmacovigilance Risk Assessment Committee activities

1. The mandate of the Pharmacovigilance Risk Assessment Committee shall cover all aspects of the risk management of the use of medicinal products for human use including the detection, assessment, minimisation and communication relating to the

risk of adverse reactions, having due regard to the therapeutic effect of the medicinal product for human use, the design and evaluation of post-authorisation safety studies and pharmacovigilance audit.

2. The Pharmacovigilance Risk Assessment Committee shall be composed of the following:

   (a) one member and one alternate member appointed by each Member State, in accordance with paragraph 3;

   (b) six members appointed by the Commission, with a view to ensuring that the relevant expertise is available within the Committee, including clinical pharmacology and pharmacoepidemiology, on the basis of a public call for expressions of interest;

   (c) two members and two alternate members appointed by the Commission, on the basis of a public call for expressions of interest, after consulting the European Parliament, in order to represent healthcare professionals;

   (d) two members and two alternate members appointed by the Commission, on the basis of a public call for expressions of interest, after consulting the European Parliament, in order to represent patient organisations.

   The alternate members shall represent and vote for the members in their absence. The alternate members referred to in point (a) may be appointed to act as rapporteurs in accordance with Article 152.

3. A Member State may delegate its tasks in the Pharmacovigilance Risk Assessment Committee to another Member State. Each Member State may represent no more than one other Member State.

4. The members and alternate members of the Pharmacovigilance Risk Assessment Committee shall be appointed on the basis of their relevant expertise in pharmacovigilance matters and risk assessment of medicinal products for human use, in order to guarantee the highest levels of specialist qualifications and a broad spectrum of relevant expertise. For this purpose, Member States shall liaise with the Management Board and the Commission in order to ensure that the final composition of the Committee covers the scientific areas relevant to its tasks.

5. The members and alternate members of the Pharmacovigilance Risk Assessment Committee shall be appointed for a term of 3 years, which may be renewed following the procedures referred to in paragraph 1. The Committee shall elect its chairperson and vice-chairperson from among its members for a term of three years, which may be prolonged once.

Article 150

Scientific working parties and scientific advisory groups

1. The scientific committees referred to in Article 146 may establish scientific working parties and scientific advisory groups in connection with the performance of their tasks.

   The scientific committees may rely on scientific working parties for the performance of certain tasks. The scientific committees shall retain the final responsibility for the assessment or any scientific opinion related to these tasks.

Working parties established by the Committee for Veterinary Medicinal Products are governed by Regulation (EU) 2019/6.

2. The Committee for Human Medicinal Products shall establish for the evaluation of specific types of medicinal products or treatments, working parties with scientific expertise in the fields of pharmaceutical quality, methodologies, non-clinical and clinical evaluations.

   For the provision of scientific advice the Committee for Human Medicinal Products shall establish a scientific advice working party.

   The Committee may establish an Environmental Risk Assessment working party and other scientific working parties, as necessary.

3. The composition of the working party and the selection of members shall be based on the following criteria:

   (a) a high level of scientific expertise;

   (b) meeting the needs for the specific multi-disciplinary expertise of the working party to which they will be appointed.

   The majority of the members of the working parties shall consist of experts from the competent authorities of the Member States. Where appropriate, the Committee for Human Medicinal Products may, following consultation with the Management Board, set a minimum number of experts from the competent authorities in a working party.

4. Competent authorities of the Member States that are not represented in a working party may request to attend meetings of working parties as an observer.

5. The Agency shall make documents discussed in working parties accessible to all competent authorities of the Member States.

6. When establishing working parties and scientific advisory groups, the scientific committees shall in their rules of procedures provide for:

   (a) the appointment of members of these working parties and scientific advisory groups on the basis of the lists of experts referred to in Article 151(2); and

   (b) consultation of these working parties and scientific advisory groups.

Article 151

Scientific experts

1. The Agency or any of the committees referred to in Article 142 may use the services of experts and service providers for the discharge of specific tasks for which they are responsible.

2. Member States shall transmit to the Agency the names of national experts with proven experience in the evaluation of medicinal products for human use and veterinary medicinal products who, taking into account conflicts of interest pursuant to Article 147, would be available to serve on working parties or scientific advisory groups of any of the committees referred to in Article 142, together with an indication of their qualifications and specific areas of expertise.

3. Where necessary, for the nomination of other experts the Agency may publish a call for expression of interest after endorsement by the Management Board of the

necessary criteria and fields of expertise, in particular to ensure a high level of public health and animal protection.

The Management Board shall adopt the appropriate procedures on a proposal from the Executive Director.

4. The Agency shall establish and maintain a pool of accredited experts. That expert pool shall include the national experts referred to in paragraph 2 and any other experts appointed by the Agency or the Commission, and shall be updated.

5. Accredited experts shall have access to training provided by the Agency, as appropriate.

6. Rapporteurs of any of the committees referred to in Article 142 may use the services of accredited experts for the fulfilment of their tasks in accordance with Article 152. Any remuneration of such accredited expert shall be deducted from the remuneration due to the rapporteurs.

7. The remuneration of experts and service providers for services used by the Agency under paragraph 1 shall be financed through the Agency's budget, in accordance with the financial rules applicable to the Agency.

Article 152

Rapporteurship

1. Where, in accordance with this Regulation, any of the Committees referred to in Article 142 is required to evaluate a medicinal product for human use, it shall appoint one of its members to act as rapporteur, taking into account existing expertise in the Member State. The Committee concerned may appoint a second member to act as co-rapporteur.

A member of a Committee shall not be appointed rapporteur for a particular case if they declare, in accordance with Article 147 any interest that might be, or might be perceived as, prejudicial to the impartial assessment of that case. The Committee concerned may replace the rapporteur or co-rapporteur by another member at any time, if they are unable to fulfil their duties within the prescribed time limits, or if an actual or potential prejudicial interest is detected.

A rapporteur appointed for that purpose by the Pharmacovigilance Risk Assessment Committee shall closely collaborate with the rapporteur appointed by the Committee for Medicinal Products for Human Use or the Reference Member State for the medicinal product for human use concerned.

When consulting the scientific advisory groups referred to in Article 150, the Committee shall forward to them the draft assessment report or reports drawn up by the rapporteur or the co-rapporteur. The opinion issued by the scientific advisory group shall be forwarded to the chairperson of the relevant committee in such a way as to ensure that the deadlines laid down in Article 6 are met.

The substance of the opinion shall be included in the assessment report published pursuant to Article 16(3).

2. Without prejudice to Article 151(7), the provision of services by rapporteurs or experts shall be governed by a written contract between the Agency and the person concerned, or where appropriate between the Agency and its employer.

The person concerned, or their employer, shall be remunerated in accordance with [a scale of fees to be included in the financial arrangements established by the Management Board/mechanism under the new fee legislation].

The first and second subparagraphs shall also apply:

(a) to the services provided by the chairpersons of the scientific committees of the Agency; and

(b) to the work of rapporteurs in the coordination group as regards the fulfilment of its tasks in accordance with Articles 108, 110, 112, 116 and 121 of [revised Directive 2001/83/EC].

Article 1

Methods to determine added therapeutic value

At the request of the Commission, the Agency shall, in respect of authorised medicinal products for human use, collect any available information on methods that Member States' competent authorities use to determine the added therapeutic value that any new medicinal product for human use provides.

SECTION 3

FINANCIAL PROVISIONS

Article 154

Adoption of the budget of the Agency

1. Estimates of all the revenue and expenditure of the Agency shall be prepared for each financial year, corresponding to the calendar year, and shall be shown in the budget of the Agency.

2. The revenue and expenditure shown in the budget shall be in balance.

3. The Agency's revenue shall consist of:

(a) a contribution from the Union;

(b) a contribution from third countries participating in the work of the Agency with which the Union has concluded international agreements for that purpose;

(c) fees paid by undertakings and entities not engaged in an economic activity:

(i) for obtaining and maintaining Union marketing authorisations for medicinal products for human use and for veterinary medicinal products and for other services provided by the Agency, as provided for in this Regulation and in Regulation (EU) 2019/6; and

(ii) for services provided by the coordination group as regards the fulfilment of its tasks in accordance with Articles 108, 110, 112, 116 and 121 of [revised Directive 2001/83/EC];

(d) charges for other services provided by the Agency;

(e) Union funding in the form of grants for participation in research and assistance projects, in accordance with the Agency's financial rules referred to in Article

155(11) and with the provisions of the relevant instruments supporting the policies of the Union.

The European Parliament and the Council ('the budgetary authority') shall re-examine, when necessary, the level of the Union contribution, referred to in the first subparagraph, point (a), on the basis of an evaluation of needs and by taking account of the level of revenue provided by the sources referred to in the first subparagraph, points (c), (d) and (e).

4. Activities relating to the assessment of marketing authorisation applications, subsequent variations, pharmacovigilance, to the operation of communications networks and to market surveillance shall be under the permanent control of the Management Board in order to guarantee the independence of the Agency. This shall not preclude the Agency from charging fees to marketing authorisation holders for performing these activities by the Agency on the condition that its independence is strictly guaranteed.

5. The expenditure of the Agency shall include staff remuneration, administrative and infrastructure costs, and operational expenditure. In respect of operational expenditure, budgetary commitments for actions which extend over more than one financial year may be broken down over several years into annual instalments, as necessary.

The Agency may award grants related to the fulfilment of the tasks incumbent upon it under this Regulation or other relevant Union legal acts or related to the fulfilment of other entrusted tasks.

6. Each year the Management Board, on the basis of a draft drawn up by the Executive Director, shall produce an estimate of revenue and expenditure for the Agency for the following financial year. That estimate, which shall include a draft establishment plan, shall be forwarded by the Management Board to the Commission by 31 March at the latest.

7. The estimate shall be forwarded by the Commission to the budgetary authority together with the preliminary draft general budget of the European Union.

8. On the basis of the estimate, the Commission shall enter in the preliminary draft general budget of the European Union the estimates it deems necessary for the establishment plan and the amount of the subsidy to be charged to the general budget, which it shall place before the budgetary authority in accordance with Article 272 of the Treaty.

9. The budgetary authority shall authorise the appropriations for the subsidy to the Agency.

The budgetary authority shall adopt the establishment plan for the Agency.

10. The budget shall be adopted by the Management Board. It shall become final following final adoption of the general budget of the European Union. Where appropriate, it shall be adjusted accordingly.

11. Any modification of the establishment plan and of the budget shall be the subject of an amending budget, which is forwarded for the purposes of information to the budgetary authority.

12. The Management Board shall, as soon as possible, notify the budgetary authority of its intention to implement any project which may have significant financial

implications for the funding of its budget, in particular any projects relating to property such as the rental or purchase of buildings. It shall inform the Commission thereof.

Where a branch of the budgetary authority has notified its intention to deliver an opinion, it shall forward its opinion to the Management Board within a period of six weeks from the date of notification of the project.

Article 155

Implementation of the Agency's budget

1. The Executive Director shall implement the budget of the Agency in accordance with Regulation (EU, Euratom) 2018/1046 of the European Parliament and of the Council[40].

2. By 1 March of financial year n+1, the Agency's accounting officer shall send the provisional accounts for year n to the Commission's accounting officer and to the Court of Auditors.

3. By 31 March of financial year n+1, the Executive Director shall send the report on the budgetary and financial management for year n to the European Parliament, to the Council, to the Commission and to the Court of Auditors.

4. By 31 March of financial year n+1, the Commission's accounting officer shall send the Agency's provisional accounts for year n, consolidated with the Commission's provisional accounts, to the Court of Auditors.

   On receipt of the Court of Auditors' observations on the Agency's provisional accounts pursuant to Article 246 of Regulation (EU, Euratom) 2018/1046, the Agency's accounting officer shall draw up the Agency's final accounts and the Executive Director shall submit them to the Management Board for an opinion.

5. The Management Board shall deliver an opinion on the Agency's final accounts for year n.

6. The Agency's accounting officer shall, by 1 July of financial year n+1, send the final accounts, together with the Management Board's opinion, to the European Parliament, to the Council, to the Court of Auditors and to the Commission's accounting officer.

7. The final accounts for year n shall be published in the *Official Journal of the European Union* by 15 November of financial year n+1.

8. The Executive Director shall send to the Court of Auditors a reply to its observations by 30 September of financial year n+1. The Executive Director shall also send that reply to the Management Board.

9. The Executive Director shall submit to the European Parliament, at the latter's request, any information required for the smooth application of the discharge

[40] Regulation (EU, Euratom) 2018/1046 of the European Parliament and of the Council of 18 July 2018 on the financial rules applicable to the general budget of the Union, amending Regulations (EU) No 1296/2013, (EU) No 1301/2013, (EU) No 1303/2013, (EU) No 1304/2013, (EU) No 1309/2013, (EU) No 1316/2013, (EU) No 223/2014, (EU) No 283/2014, and Decision No 541/2014/EU and repealing Regulation (EU, Euratom) No 966/2012 (OJ L 193, 30.7.2018, p. 1).

procedure for the financial year concerned, as laid down in Article 261(3) of Regulation (EU, Euratom) 2018/1046.

10. The European Parliament, upon a recommendation from the Council, shall, before 15 May of financial year n+2, give a discharge to the Executive Director in respect of the implementation of the budget for year n.

11. The financial rules applicable to the Agency shall be adopted by the Management Board after the Commission has been consulted. They shall not depart from Commission Delegated Regulation (EU) 2019/715[41] unless specifically required for the Agency's operation and with the Commission's prior consent.

Article 156

Fraud prevention

1. In order to combat fraud, corruption and other unlawful activities, the Regulation (EU, Euratom) No 883/2013 of the European Parliament and of the Council[42] shall apply without restriction.

2. The Agency shall accede to the Interinstitutional Agreement of 25 May 1999 between the European Parliament, the Council of the European Union and the Commission of the European Communities[43] and shall adopt, without delay, the appropriate provisions applicable to all the employees of the Agency using the template set out in the Annex to that Agreement.

3. The European Court of Auditors shall have the power of audit, on the basis of documents and on the spot, over all grant beneficiaries, contractors and subcontractors who have received Union funds from the Agency.

4. OLAF may carry out investigations, including on-the-spot checks and inspections with a view to establishing whether there has been fraud, corruption or any other illegal activity affecting the financial interests of the Union in connection with a grant or a contract funded by the Agency, in accordance with the provisions and procedures laid down in Regulation (EU, Euratom) No 883/2013 and Council Regulation (Euratom, EC) No 2185/96[44].

5. Working agreements with third countries and international organisations, contracts, grant agreements and grant decisions of the Agency shall contain provisions expressly empowering the European Court of Auditors and OLAF to conduct such audits and investigations, according to their respective competences.

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41 Commission Delegated Regulation (EU) 2019/715 of 18 December 2018 on the framework financial regulation for the bodies set up under the TFEU and Euratom Treaty and referred to in Article 70 of Regulation (EU, Euratom) 2018/1046 of the European Parliament and of the Council (OJ L 122, 10.5.2019, p. 1).

42 Regulation (EU, Euratom) No 883/2013 of the European Parliament and of the Council of 11 September 2013 concerning investigations conducted by the European Anti-Fraud Office (OLAF) and repealing Regulation (EC) No 1073/1999 of the European Parliament and of the Council and Council Regulation (Euratom) No 1074/1999 (OJ L 248, 18.9.2013, p. 1).

43 Interinstitutional Agreement of 25 May 1999 between the European Parliament, the Council of the European Union and the Commission of the European Communities concerning internal investigations by the European Anti-fraud Office (OLAF) (OJ L 136, 31.5.1999, p. 15).

44 Council Regulation (Euratom, EC) No 2185/96 of 11 November 1996 concerning on-the-spot checks and inspections carried out by the Commission in order to protect the European Communities' financial interests against fraud and other irregularities (OJ L 292, 15.11.1996, p. 2).

6. In accordance with Council Regulation (EU) 2017/1939[45], the EPPO may investigate and prosecute fraud and other illegal activities affecting the financial interests of the Union as provided for in Directive (EU) 2017/1371 of the European Parliament and of the Council[46].

SECTION 4

GENERAL PROVISIONS GOVERNING THE AGENCY

Article 157

Liability

1. The contractual liability of the Agency shall be governed by the law applicable to the contract in question. The Court of Justice of the European Union shall have jurisdiction pursuant to any arbitration clause contained in a contract concluded by the Agency.

2. In the case of non-contractual liability, the Agency shall, in accordance with the general principles common to the laws of the Member States, make good any damage caused by it or by its staff in the performance of their duties.

   The Court of Justice shall have jurisdiction in any dispute relating to compensation for any such damage.

3. The personal liability of its staff towards the Agency shall be governed by the provisions laid down in the Staff Regulations or Conditions of Employment of Other Servants applicable to them.

Article 158

Access to documents

Regulation (EC) No 1049/2001 shall apply to documents held by the Agency.

The Agency shall set up a register pursuant to Article 2(4) of Regulation (EC) No 1049/2001 to make available all documents that are publicly available pursuant to this Regulation.

The Management Board shall adopt the arrangements for implementing Regulation (EC) No 1049/2001.

Decisions taken by the Agency pursuant to Article 8 of Regulation (EC) No 1049/2001 may give rise to the lodging of a complaint with the Ombudsman or form the subject of an action before the Court of Justice, under the conditions laid down in Article 228 and Article 263 of the Treaty respectively.

Article 159

Privileges

[45] **C**ouncil Regulation (EU) 2017/1939 of 12 October 2017 implementing enhanced cooperation on the establishment of the European Public Prosecutor's Office ('the EPPO') (OJ L 283, 31.10.2017, p. 1).

[46] Directive (EU) 2017/1371 of the European Parliament and of the Council of 5 July 2017 on the fight against fraud to the Union's financial interests by means of criminal law (OJ L 198, 28.7.2017, p. 29).

Protocol No 7 on the Privileges and Immunities of the European Union annexed to the Treaty on the Functioning of the European Union shall apply to the Agency and its staff.

Article 160

Staff

The Staff Regulations and the rules adopted by agreement between the institutions of the Union for giving effect to those Staff Regulations and Conditions of Employment of Other Servants shall apply to the staff of the Agency.

The Agency may make use of seconded national experts or other staff not employed by the Agency.

The Management Board, in agreement with the Commission, shall adopt the necessary implementing provisions.

Article 161

Security rules on the protection of classified and sensitive non-classified information

The Agency shall adopt own security rules equivalent to the Commission's security rules for protecting European Union Classified Information (EUCI) and sensitive non-classified information, as set out in Commission Decisions (EU, Euratom) 2015/443[47] and 2015/444[48]. The security rules of the Agency shall cover, inter alia, provisions for the exchange, processing and storage of such information.

Members of the Management Board, the Executive Director, members of the committees, external experts participating in ad hoc working groups, and members of the staff of the Agency shall comply with the confidentiality requirements under Article 339 TFEU, even after their duties have ceased.

The Agency may take the necessary measures to facilitate the exchange of information relevant to its tasks with the Commission and the Member States and, where appropriate, the relevant Union institutions, bodies, offices and agencies. Any administrative arrangements concluded to that end with regard to the sharing of EU classified information (EUCI) or, in the absence of such arrangements, any exceptional ad hoc release of EUCI, shall have received the Commission’s prior approval.

Article 162

Consultation process

1. The Agency shall establish a consultation process with relevant national authorities or bodies for the exchange of information and pooling of knowledge on general issues of scientific or technical nature related to the tasks of the Agency, in particular guidelines on unmet medical needs and the design of clinical trials, other studies and the generation of evidence along the life cycle of medicinal products.

[47] Commission Decision (EU, Euratom) 2015/443 of 13 March 2015 on Security in the Commission (OJ L 72, 17.3.2015, p. 41).

[48] Commission Decision (EU, Euratom) 2015/444 of 13 March 2015 on the security rules for protecting EU classified information (OJ L 72, 17.3.2015, p. 53).

The consultation process shall include bodies responsible for health technology assessment as referred to in Regulation (EU) 2021/2282 and national bodies responsible for pricing and reimbursement.

The conditions of participation shall be set by the Management Board in agreement with the Commission.

2. The Agency may extend the consultation process to patients, medicine developers, healthcare professionals, industries or other stakeholders, as relevant.

Article 163

Contacts with civil society representatives

The Management Board shall, in agreement with the Commission, develop appropriate contacts between the Agency and the representatives of the industry, consumers and patients and the healthcare professions. These contacts may include the participation of observers in certain aspects of the Agency's work, under conditions determined beforehand by the Management Board, in agreement with the Commission.

Article 164

Support to SMEs and to not-for profit entities

1. The Agency shall ensure that micro, small and medium-sized enterprises ('SMEs') and not-for-profit entities are offered a support scheme.

2. The support scheme shall be comprised of regulatory, procedural and administrative support and reduction, deferral or waivers of fees.

3. The scheme shall cover the various steps involved in pre-authorisation procedures, and in particular scientific advice, the submission of the marketing authorisation application, and the post-authorisation procedures.

4. SMEs shall benefit from the incentives laid down in Commission Regulation (EC) No 2049/2005 and [revised Council Regulation (EC) No 297/95][49].

5. For not-for-profit entities, the Commission shall adopt specific provisions clarifying the definitions, establishing waivers, reductions or deferrals of fees, as appropriate, in accordance with the procedure referred to in Article 10 and Article 12 of [revised Regulation (EC) No 297/95].

Article 165

Transparency

To ensure an appropriate level of transparency, the Management Board shall, on the basis of a proposal by the Executive Director and in agreement with the Commission, adopt rules to ensure the availability to the public of regulatory, scientific or technical information concerning the authorisation or supervision of medicinal products for human use which is not of a confidential nature.

[49] Council Regulation (EC) No 297/95 of 10 February 1995 on fees payable to the European Agency for the Evaluation of Medicinal Products (OJ L 35, 15.2.1995, p. 1).

The internal rules and procedures of the Agency, its committees and its working groups shall be made available to the public at the Agency and on the Internet.

The Agency may engage in communication activities on its own initiative within its field of competence. The allocation of resources to communication activities shall not be detrimental to the effective exercise of the tasks of the Agency. Communication activities shall be carried out in accordance with relevant communication and dissemination plans adopted by the Management Board.

Article 166

Personal health data

1. To support its public health tasks and in particular the evaluation and monitoring medicinal products or the preparation of regulatory decisions and scientific opinions, the Agency may process personal health data, from sources other than clinical trials, for the purpose of improving the robustness of its scientific assessment or verifying claims of the applicant or marketing authorisation holder in the context of the evaluation or supervision of medicinal product.

2. The Agency may consider and decide upon additional evidence available, independently from the data submitted by the marketing authorisation applicant or marketing authorisation holder. On that basis, the summary of product characteristics shall be updated if the additional evidence has an impact on the benefit-risk balance of a medicinal product.

3. The Agency shall adopt adequate data governance practices and the required standards to ensure the appropriate use and protection of personal health data, in accordance with this Regulation and Regulation (EU) 2018/1725.

Article 167

Protection against cyber attacks

The Agency shall equip itself with a high level of security controls and processes against cyber attacks, cyber espionage and other data breaches to ensure the protection of health data and the normal functioning of the Agency at all times, especially during public health emergencies or major events at Union level.

For the purposes of the first subparagraph, the Agency shall actively identify and implement cybersecurity best practices adopted within Union institutions, bodies, offices and agencies for preventing, detecting, mitigating, and responding to cyber attacks.

Article 168

Confidentiality

1. Unless otherwise provided for in this Regulation and without prejudice to Regulation (EC) No 1049/2001 and Directive (EU) 2019/1937 of the European Parliament and of the Council[50], and existing national provisions and practices in the Member States on confidentiality, all parties involved in the application of this Regulation shall respect the confidentiality of information and data obtained in carrying out their tasks

[50] Directive (EU) 2019/1937 of the European Parliament and of the Council of 23 October 2019 on the protection of persons who report breaches of Union law (OJ L 305, 26.11.2019, p. 17).

in order to protect the commercially confidential information and trade secrets of natural or legal persons in accordance with Directive (EU) 2016/943 of the European Parliament and of the Council[51], including intellectual property rights.

2. Without prejudice to paragraph 1, all parties involved in the application of this Regulation shall ensure that no commercially confidential information is shared in a way which has the potential to enable undertakings to restrict or distort competition within the meaning of Article 101 TFEU.

3. Without prejudice to paragraph 1, information exchanged on a confidential basis between competent authorities of the Member States and between competent authorities of the Member States and the Commission and the Agency shall not be disclosed without the prior agreement of the authority from which that information originates.

4. Paragraphs 1, 2 and 3 do not affect the rights and obligations of the Commission, the Agency, Member States or other actors identified in this Regulation with regard to the exchange of information and the dissemination of warnings, nor do they affect the obligations of the persons concerned to provide information under criminal law.

5. The Commission, the Agency, and Member States may exchange commercially confidential information with regulatory authorities of third countries with which they have concluded bilateral or multilateral confidentiality arrangements.

Article 169

Processing of personal data

1. The Agency may process personal data, including personal health data, for the performance of its tasks as referred to in Article 135, in particular for the purpose of improving the robustness of its scientific assessment or verifying claims of the applicant or marketing authorisation holder in the context of the evaluation or supervision of medicinal products.

   Additionally, the Agency may process such data for the performance of regulatory science activities, as defined in paragraph 2, provided that the processing of those personal data:

   (a) is strictly required and duly justified to achieve the objectives of the project or of the horizon scanning activities concerned;

   (b) as regards special categories of personal data, is strictly necessary and subject to appropriate safeguards, which may include pseudonymisation.

2. For the purpose of this Article, ‘regulatory science activities’ shall mean scientific projects to complement available scientific evidence with regard to diseases or horizontal questions related to medicinal products, to fill evidence gaps that cannot be fully addressed through data in the possession of the Agency, or to support horizon scanning activities.

3. The processing of personal data by the Agency in the context of this Article shall be guided by the principles of transparency, explainability, fairness, and accountability.

[51] Directive (EU) 2016/943 of the European Parliament and of the Council of 8 June 2016 on the protection of undisclosed know-how and business information (trade secrets) against their unlawful acquisition, use and disclosure (OJ L 157, 15.6.2016, p. 1).

4. The Management Board shall establish the general scope for the regulatory science activities in consultation with the Commission and the European Data Protection Supervisor.

5. The Agency shall keep documentation containing a detailed description of the process and of the rationale behind the training, testing and validation of algorithms to ensure transparency of the process and the algorithms, including their compliance with the safeguards provided for in this Article, and to allow for verification of the accuracy of the results based on the use of such algorithms. Upon request, the Agency shall make relevant documentation available to interested parties, including Member States.

6. If the personal data to be processed for the regulatory science activities have been directly provided by a Member State, a Union body, a third country or an international organisation, the Agency shall request authorisation from that provider of data, unless the provider of data has granted its prior authorisation to such processing for the purpose of regulatory science activities, either in general terms or subject to specific conditions.

7. Processing of personal data under this Regulation shall be subject to Regulations (EU) 2016/679 and (EU) 2018/1725, as applicable.

Article 170

Evaluation

1. Not later than [*note to OP = five years after the date of entry into application*], and every 10 years thereafter, the Commission shall commission an evaluation of the Agency's performance in relation to its objectives, mandate, tasks, governance and location(s) in accordance with Commission's guidelines.

2. The evaluation shall, in particular, address the possible need to modify the mandate of the Agency, and the financial implications of any such modification.

3. On the occasion of every second evaluation, there shall be an assessment of the results achieved by the Agency having regard to its objectives, mandate, governance and tasks, including an assessment of whether the continuation of the Agency is still justified with regard to these objectives, mandate, governance and tasks. This assessment shall also include the experience acquired as a result of the operation of the procedures laid down in this Regulation and in Chapter III, Sections 4 and 5 of [revised Directive 2001/83/EC] on the basis of input from Member States and the Coordination group referred to in Article 37 of [revised Directive 2001/83/EC].

4. The Commission shall report to the European Parliament, the Council and the Management Board on the evaluation findings. The findings of the evaluation shall be made public.

5. By 10 years following the entering into application, the Commission shall assess the application of this Regulation and produce an evaluation report on the progress towards achievement of the objectives contained herein including an assessment of the resources required to implement this Regulation.

CHAPTER XII
GENERAL PROVISIONS

Article 171

Penalties at national level

1. Member States shall lay down the rules on penalties applicable to infringements of this Regulation and shall take all measures necessary to ensure that they are implemented. The penalties provided for shall be effective, proportionate and dissuasive. Member States shall, without delay, notify the Commission of those rules and of those measures and shall notify it, without delay, of any subsequent amendment affecting them.

2. Member States shall inform the Commission immediately of any litigation instituted for infringement of this Regulation.

Article 172

Union penalties

1. The Commission may impose financial penalties in the form of fines or periodic penalty payments on the marketing authorisations holder granted under this Regulation if they fail to comply with any of the obligations laid down in Annex II in connection with the marketing authorisations.

2. The Commission may, insofar as specifically provided for in the delegated acts referred to in paragraph 10, point (b), impose the financial penalties referred to in paragraph 1 on a legal entity or legal entities other than the marketing authorisation holder provided that such entities form part of the same economic entity as the marketing authorisation holder and that such other legal entities:

   (a) exerted a decisive influence over the marketing authorisation holder; or

   (b) were involved in, or could have addressed, such failure to comply with the obligation by the marketing authorisation holder.

3. Where the Agency or a competent authority of a Member State is of the opinion that a marketing authorisation holder has failed to comply with any of the obligations, referred to in paragraph 1, it may request the Commission to investigate whether to impose financial penalties pursuant to that paragraph.

4. In determining whether to impose a financial penalty and in determining its appropriate amount, the Commission shall be guided by the principles of effectiveness, proportionality and dissuasiveness and take into consideration, where relevant, the seriousness and the effects of the failure to comply with the obligations.

5. For the purposes of paragraph 1, the Commission shall take into account:

   (a) any infringement procedure initiated by a Member State against the same marketing authorisation holder on the basis of the same legal grounds and the same facts;

   (b) any sanctions, including penalties, already imposed on the same marketing authorisation holder on the basis of the same legal grounds and the same facts.

6. Where the Commission finds that the marketing authorisation holder has failed, intentionally or negligently, to comply with its obligations, as referred to in paragraph 1, it may adopt a decision imposing a fine not exceeding 5 % of the marketing authorisation holder's Union turnover in the business year preceding the date of that decision.

Where the marketing authorisation holder continues to fail to comply with its obligations referred to in paragraph 1, the Commission may adopt a decision imposing periodic penalty payments per day not exceeding 2,5 % of the marketing authorisation holder's average daily Union turnover in the business year preceding the date of that decision.

Periodic penalty payments may be imposed for a period running from the date of notification of the relevant Commission's decision until the failure to comply with the obligation by the marketing authorisation holder, as referred to in paragraph 1, has been brought to an end.

7. When conducting the investigation on a failure to comply with any of the obligations referred to in paragraph 1, the Commission may cooperate with competent authorities of the Member States and rely on resources provided by the Agency.

8. Where the Commission adopts a decision imposing a financial penalty, it shall publish a concise summary of the case, including the names of the marketing authorisation holders involved and the amounts of and reasons for the financial penalties imposed, having regard to the legitimate interest of the marketing authorisation holders for the protection of their business secrets.

9. The Court of Justice of the European Union shall have unlimited jurisdiction to review decisions whereby the Commission has imposed financial penalties. The Court of Justice of the European Union may cancel, reduce or increase the fine or periodic penalty payment imposed by the Commission.

10. The Commission is empowered to adopt delegated acts in accordance with Article 175 in order to supplement this Regulation by laying down:

(a) procedures to be applied by the Commission when imposing fines or periodic penalty payments, including rules on the initiation of the procedure, measures of inquiry, rights of the defence, access to file, legal representation and confidentiality;

(b) further detailed rules on the imposition by the Commission of financial penalties on legal entities other than the marketing authorisation holder;

(c) rules on duration of procedure and limitation periods;

(d) elements to be taken into account by the Commission when setting the level of and imposing fines and periodic penalty payments, as well as the conditions and methods for their collection.

CHAPTER XIII
DELEGATED AND IMPLEMENTING ACTS

Article 173

Standing Committee on Medicinal Products for Human Use and examination procedure

1. The Commission shall be assisted by the Standing Committee on Medicinal Products for Human Use established by Article 214 of [revised Directive 2001/83/EC]. That committee shall be a committee within the meaning of Regulation (EU) No 182/2011.

2. Where reference is made to this paragraph, Article 5 of Regulation (EU) No 182/2011 shall apply.

3. Where the opinion of the Committee is to be obtained by written procedure and reference is made to this paragraph, that procedure shall be terminated without result only when, within the time-limit for delivery of the opinion, the chair of the Committee so decides.

4. The Standing Committee on Medicinal Products for Human Use shall ensure that its rules of procedure are adapted to the need to make medicinal products swiftly available to patients.

Article 174

Implementing measures related to authorisation and pharmacovigilance activities

1. In order to harmonise electronic transmissions provided for in this Regulation, the Commission may adopt implementing measures covering the format and content of electronic transmissions by marketing authorisation holders.

   Those measures shall take account of the work on international harmonisation carried out in the area and shall, where necessary, be revised to take account of technical and scientific progress. Those measures shall be adopted in accordance with the examination procedure referred to in Article 173(2).

2. In order to harmonise the performance of the pharmacovigilance activities provided for in this Regulation, the Commission shall adopt implementing measures as provided for in Article 214 of [revised Directive 2001/83/EC] covering the following areas:

   (a) the content and maintenance of the pharmacovigilance system master file kept by the marketing authorisation holder;

   (b) the minimum requirements for the quality system for the performance of pharmacovigilance activities by the Agency;

   (c) the use of internationally agreed terminology, formats and standards for the performance of pharmacovigilance activities;

   (d) the minimum requirements for the monitoring of data included in the Eudravigilance database to determine whether there are new risks or whether risks have changed;

   (e) the format and content of electronic transmission of suspected adverse reactions by Member States and marketing authorisation holders;

   (f) the format and content of electronic periodic safety update reports and risk management plans;

   (g) the format of protocols, abstracts and final study reports of the post-authorisation safety studies.

   Those measures shall take account of the work on international harmonisation carried out in the area of pharmacovigilance and shall, where necessary, be revised to take

account of technical and scientific progress. Those measures shall be adopted in accordance with the examination procedure referred to in Article 173(2).

Article 175

Exercise of the delegation

1. The power to adopt delegated acts is conferred on the Commission subject to the conditions laid down in this Article.

2. The power to adopt delegated acts referred to in Articles 3(5), 19(8), 21, 47(4), 49(2), 63(2), 67(4), 75(3), 81(4) and 172(10) shall be conferred on the Commission for a period of five years from [date of entry into force]. The Commission shall draw up a report in respect of the delegation of power not later than nine months before the end of the five-year period. The delegation of power shall be tacitly extended for periods of an identical duration, unless the European Parliament or the Council opposes such extension not later than three months before the end of each period.

3. The delegation of power referred to in Articles 3(5), 19(8), 21, 47(4), 49(2), 63(2), 67(4), 75(3), 81(4) and 172(10) may be revoked at any time by the European Parliament or by the Council. A decision to revoke shall put an end to the delegation of the power specified in that decision. It shall take effect the day following the publication of the decision in the *Official Journal of the European Union* or at a later date specified therein. It shall not affect the validity of any delegated acts already in force.

4. Before adopting a delegated act, the Commission shall consult experts designated by each Member State in accordance with the principles laid down in the Interinstitutional Agreement of 13 April 2016 on Better Law-Making.

5. As soon as it adopts a delegated act, the Commission shall notify it simultaneously to the European Parliament and to the Council.

6. A delegated act adopted pursuant to Articles 21, 19(8), 47(4), 49(2) and 175 shall enter into force only if no objection has been expressed either by the European Parliament or by the Council within a period of two months of notification of that act to the European Parliament and to the Council or if, before the expiry of that period, the European Parliament and the Council have both informed the Commission that they will not object. That period shall be extended by three months at the initiative of the European Parliament or of the Council.

CHAPTER XIV
AMENDMENTS TO OTHER LEGAL ACTS

Article 176

Amendments to Regulation (EC) No 1394/2007

Regulation (EC) No 1394/2007 is amended as follows:

(1) Articles 8, 17 and 20 to 23 are deleted;

(2) in Article 9(3), the fourth subparagraph is replaced by the following:

‘If the application does not include the results of the assessment, the Agency shall seek an opinion on the conformity of the device part with Annex I to Regulation (EU) 2017/745 of the European Parliament and of the Council* from a notified body

identified in conjunction with the applicant, unless the Committee for Medicinal Products for Human Use advised by its experts for medical devices decides that involvement of a notified body is not required.

*Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (OJ L 117, 5.5.2017, p. 1).'

Article 177

Amendments to Regulation (EU) No 536/2014

Regulation (EU) No 536/2014 is amended as follows:

(1) the following Article 5a is inserted:

'*Article 5a*

Environmental risk assessment for investigational medicinal products for human use containing or consisting of genetically modified organisms

1. Where the application according to Article 5 of this Regulation concerns clinical trials with investigational medicinal products for human use containing or consisting of genetically modified organisms (GMOs) within the meaning of Article 2 of Directive 2001/18/EC of the European Parliament and of the Council*, the sponsor shall submit an environmental risk assessment (ERA) in the EU portal (CTIS).

2. The ERA referred to in paragraph 1 shall be conducted in accordance with the principles set out in Annex II to Directive 2001/18/EC and the scientific guidelines developed by the Agency in coordination with the competent authorities of the Member States, established according to Directive 2001/18/EC for this purpose and the delegated act referred to in paragraph 8.

3. Articles 6 to 11 of Directive 2001/18/EC shall not apply to investigational medicinal products for human use containing or consisting of genetically modified organisms.

4. The Committee for Medicinal Products for Human Use (CHMP) shall assess the ERA referred to in paragraph 1 in the form of a scientific opinion. The CHMP shall submit its opinion to the competent authority of the Reporting Member State within 45 days from the validation date referred to in Article 5(3). Where appropriate, the opinion shall include risk mitigation measures. The sponsor shall provide evidence to the Reporting Member State and the Member States Concerned that these measures will be implemented.

5. The CHMP may request, with justified reasons, via the EU portal (CTIS) additional information from the sponsor regarding the assessment referred to in paragraph 1, which shall be provided only within the period referred to in paragraph 5.

6. To obtain and review the additional information referred to in paragraph 6, the Agency may extend the period referred to in paragraph 5 by a maximum of 31 days. The sponsor shall submit the requested additional information within the period set by the Agency. Where the sponsor does not provide additional

information within the period set by the Agency, the application referred to in paragraph 1 shall be deemed to have expired in all Member States concerned.

7. In case of first-in-class products or when a novel question arises during the assessment of the submitted ERA as referred to in paragraph 1, the Agency shall consult with bodies that Member States have set up in accordance with Directive 2001/18/EC or Directive 2009/41/EC of the European Parliament and of the Council**. If a consultation is necessary, the technical dossier addressing in sufficient detail the information specified in Annex III to Directive 2001/18/EC should be included to support the ERA where appropriate.

8. The Commission shall be empowered to adopt a delegated act in accordance with Article 89 to amend the Annexes to this Regulation in order to specify the procedure for the submission and the harmonized assessment of the ERA for investigational medicinal products containing or consisting of GMOs as set out in paragraphs 1 to 8.

The delegated act referred to in the first subparagraph shall establish that the ERA is an independent part of the application.

The delegated act referred to in the first subparagraph shall specify the content of the ERA taking into account the common application forms and Good Practice Documents for genetically modified human cells and for adeno-associated viral vectors that were published by the Agency.

The delegated act referred to in the first subparagraph shall contain a provision to update the ERA requirements for investigational medicinal products containing or consisting of GMOs following scientific developments and changes of (Directive 2001/18/EC).';

* Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC - Commission Declaration (OJ L 106, 17.4.2001, p. 1).

** Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the contained use of genetically modified micro-organisms (Recast) (OJ L 125, 21.5.2009, p. 75).';

(2) in Article 25(1), point (d), is replaced by the following:

'(d) measures to protect subjects, third persons and the environment;';

(3) Article 26 is replaced by the following:

'*Article 26*

Language requirements

The language of the application dossier, or parts thereof, shall be determined by the Member State concerned.

The language for the environmental risk assessment (ERA) shall preferably be English.

Member States, in applying the first subparagraph, shall consider accepting, for the documentation not addressed to the subject, a commonly understood language in the medical field.';

(4) in Article 37(4), the following subparagraph is inserted after the first subparagraph:

In the case of a clinical trial which involves the use of a medicinal product in the paediatric population, the timeline referred to in the first subparagraph to submit to the EU database a summary of the results of the clinical trial shall be 6 months.';

(5) in Article 61(2), point (a), is replaced by the following:

'(a) it shall have at its disposal, for manufacture or import, suitable and sufficient premises, technical equipment and control facilities complying with the requirements set out in this Regulation and, where appropriate, in case of investigational medicinal products containing or consisting of GMOs, in Directive 2009/41/EC;';

(6) in Article 66(1), point (c), is replaced by the following:

(c) information to identify the medicinal product, including, where appropriate, 'This IMP contains genetically modified organisms;';

(7) in Article 76, paragraph (1) is replaced by the following:

'1. Member States shall ensure that systems for compensation for any damage suffered by a subject resulting from the participation in a clinical trial or caused to third persons or the environment during such trial conducted on their territory are in place in the form of insurance, a guarantee, or a similar arrangement that is equivalent as regards its purpose and which is appropriate to the nature and the extent of the risk.';

(8) Article 89 is replaced by the following:

'*Article 89*

Exercise of the delegation

1. The power to adopt delegated acts is conferred on the Commission subject to the conditions laid down in this Article.

2. The power to adopt delegated acts referred to in Articles 5a, 27, 39, 45, 63(1) and 70 shall be conferred on the Commission for a period of five years from the date referred to in Article 99(2). The Commission shall draw up a report in respect of the delegated powers not later than nine months before the end of the five year period. The delegation of powers shall be tacitly extended for periods of an identical duration, unless the European Parliament or the Council opposes such extension not later than three months before the end of each period.

3. The delegation of power referred to in Articles 5a, 27, 39, 45, 63(1), and 70 may be revoked at any time by the European Parliament or by the Council. A decision to revoke shall put an end to the delegation of the power specified in that decision. It shall take effect the day following the publication of the decision in the Official Journal of the European Union or at a later date specified therein. It shall not affect the validity of any delegated acts already in force.

4. Before adopting a delegated act, the Commission shall consult experts designated by each Member State in accordance with the principles laid down in the Interinstitutional Agreement of 13 April 2016 on Better Law-Making.

5. As soon as it adopts a delegated act, the Commission shall notify it simultaneously to the European Parliament and to the Council.

6. A delegated act adopted pursuant to Articles 5a, 27, 39, 45, 63(1), and 70 shall enter into force only if no objection has been expressed either by the European Parliament or the Council within a period of two months of notification of that act to the European Parliament and the Council or if, before the expiry of that period, the European Parliament and the Council have both informed the Commission that they will not object. That period shall be extended by two months at the initiative of the European Parliament or the Council.';

(9) Article 91 is replaced by the following:

'*Article 91*

Relation with other Union legal acts

'This Regulation shall be without prejudice to Council Directive 97/43/Euratom[52], Council Directive 96/29/Euratom[53], Directive 2004/23/EC of the European Parliament and of the Council[54], Directive 2002/98/EC of the European Parliament and of the Council[55] and Directive 2010/53/EU of the European Parliament and of the Council[56].

In the context of inspections referred under Articles 52(5) of [revised Regulation 726/2004] and Article 78 of this Regulation and the criteria set out in Annex III of [revised Regulation 726/2004] apply mutatis mutandis.'

Article 178

Amendments to Regulation (EU) 2022/123

Regulation (EU) No 2022/123 is amended as follows:

1. In Article 18, the following paragraph (7) is added:

'(7) Where a request has been made in accordance with Article 18(3) of Regulation (EU) 2022/123 and there is an application for a temporary emergency marketing authorisation for the medicinal product concerned in accordance with Article 30 of Regulation [Note to OP: Please fill in with the number of this Regulation]*, the procedure initiated under that Regulation shall prevail.'

* [OP: Insert the full title of that Regulation and the OJ reference, please]

2. Articles 33 and 34 are deleted.

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52 Council Directive 97/43/Euratom of 30 June 1997 on health protection of individuals against the dangers of ionizing radiation in relation to medical exposure, and repealing Directive 84/466/Euratom (OJ L 180, 9.7.1997, p. 22).

53 Council Directive 96/29/Euratom of 13 May 1996 laying down basic safety standards for the protection of the health of workers and the general public against the dangers arising from ionizing radiation (OJ L 159, 29.6.1996, p. 1).

54 Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells (OJ L 102, 7.4.2004, p. 48).

55 Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC (OJ L 033, 8.2.2003, p. 30).

56 Directive 2010/53/EU of the European Parliament and of the Council of 7 July 2010 on standards of quality and safety of human organs intended for transplantation (OJ L 207, 6.8.2010, p. 14).

CHAPTER XV
FINAL PROVISIONS

Article 179

Repeals

1. Regulations (EC) No 141/2000, (EC) No 726/2004 and (EC) No 1901/2006 are repealed.

   References to the repealed Regulations shall be construed as references to this Regulation and shall be read in accordance with the correlation table in Annex V.

2. Commission Implementing Regulation (EU) No 198/2013[57] is repealed.

Article 180

Transitional provisions

1. The provisions of Article 117 of this Regulation shall also apply to marketing authorisations of medicinal products for human use granted in accordance with Regulation (EC) No 726/2004 and in accordance with Directive 2001/83/EC before [*Note to the OP: Please insert the date = date of entry into application of this Regulation*].

2. The procedures concerning the applications for marketing authorisations for medicinal products for human use that have been validated, in accordance with Article 5 of Regulation (EC) No 726/2004, before [*Note to the OP: Please insert the date = date of entry into application of this Regulation*] and that were pending on [*Note to the OP: Please insert the date = the day before the date of application of this Regulation*] shall be completed in accordance with Article 10 of Regulation (EC) No 726/2004.

3. Procedures concerning imposed post-authorisation studies that were initiated in accordance with Article 10a of Regulation (EC) No 726/2004, before [*Note to the OP: Please insert the date = date of entry into application of this Regulation*] and that were pending on [*Note to the OP: Please insert the date = the day before the date of application of this Regulation*] shall be completed in accordance with Article 20 of this Regulation.

4. By way of derogation, the periods of regulatory protection referred to in Article 29 shall not apply to reference medicinal products for which an application for marketing authorisation has been submitted before [*Note to the OP: Please insert the date of application of this Regulation*]. Article 14(11) of Regulation (EC) No 726/2004 shall continue to apply to them.

5. Orphan designations granted before *[Note to the OP: Please insert the date of application of this Regulation]*, entered in and not removed from the Community Register of Orphan Medicinal Products in accordance with Article 5, paragraphs 8 and 12, respectively, of Regulation (EC) No 141/2000 and not granted a marketing

[57] Commission Implementing Regulation (EU) No 198/2013 of 7 March 2013 on the selection of a symbol for the purpose of identifying medicinal products for human use that are subject to additional monitoring (OJ L 65, 8.3.2013, p. 17).

authorisation in accordance with Article 7(3) of Regulation (EC) No 141/2000 corresponding to the orphan designation shall be considered to comply with this Regulation and shall be entered in the Register of Designated Orphan Medicinal Products.

6. Orphan designations granted before *[Note to the OP: Please insert the date of application of this Regulation]* which are either removed from the Community Register of Orphan Medicinal Products in accordance with Article 5(12) of Regulation (EC) No 141/2000 or granted a marketing authorisation in accordance with Article 7(3) of Regulation (EC) No 141/2000 shall not be considered as orphan designations and shall not be entered in the Register of Designated Orphan Medicinal Products.

7. The 7-year validity of an orphan designation referred to in Article 66 of this Regulation for orphan medicinal products granted before *[Note to the OP: Please insert the date of application of this Regulation],* entered in and not removed from the Community Register of Orphan Medicinal Products in accordance with Article 5 (8) and (12), respectively, of Regulation (EC) No 141/2000 and not granted a marketing authorisation in accordance with those Article 7(3) of Regulation (EC) No 141/2000 corresponding to the orphan designation shall begin to run from *[Note to the OP: Please insert the date of application of this Regulation]*.

8. The procedures concerning orphan designations which were initiated in accordance with Article 5, paragraphs 1, 11 or 12 of Regulation (EC) No 141/2000 before *[Note to the OP: Please insert the date of application of this Regulation]* and were pending on *[OP please insert the date = the day before the date of application]*, shall be completed in accordance with Article 5, paragraphs 1, 11 or 12 of Regulation (EC) No 141/2000 as applicable on [*OP please insert the date = the day before the date of application]*.

9. When a paediatric investigation plan, a waiver or a deferral has been granted in accordance with Regulation (EC) No 1901/2006 before [*Note to the OP: Please insert the date of application of this Regulation*], it shall be considered to comply with this Regulation.

   The procedures concerning the application for a paediatric investigation plan, a waiver or a deferral submitted before [date of entry into application], shall be completed in accordance with Regulation (EC) No 1901/2006.

10. Regulations (EC) No 2141/96, (EC) No 2049/2005, (EC) No 507/2006 and (EC) No 658/2007 shall remain in force and continue to apply unless and until repealed.

11. Regulation (EC) No 1234/2008 shall continue to apply unless and until repealed as regards medicinal products for human use that are covered by Regulation (EC) No 726/2004 and Directive 2001/83/EC and that are not excluded from the scope of Regulation (EC) No 1234/2008 pursuant to Article 23b, paragraphs 4 and 5 of Directive 2001/83/EC.

12. Commission Regulation (EC) No 847/2000[58] shall continue to apply unless and until repealed as regards orphan medicinal products that are covered by this Regulation.

[58] Commission Regulation (EC) No 847/2000 of 27 April 2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product

13. By way of derogation from Article [*Duration of application of Chapter III*] vouchers granted until [*Note to OP: insert the date of 15 years after the date of entry into force of this Regulation*] or until the date when the Commission has granted a total of 10 vouchers in accordance with Chapter III, whichever date is the earliest, shall continue to be valid according to the conditions set out in Chapter III.

Article 181

Entry into force

This Regulation shall enter into force on the twentieth day following that of its publication in the *Official Journal of the European Union*.

It shall apply from [*Note to the OP: Please insert the date of 18 months after its entry into force. The date should be identical to the date for the application of the Directive*].

However, Article 67 shall apply from [*Note to the OP: Please insert the date of 2 years after the date of adoption/entry into force/application of this Regulation*].

This Regulation shall be binding in its entirety and directly applicable in the Member States in accordance with the Treaties.

Done at Brussels,

For the European Parliament	*For the Council*
The President	*The President*

and definitions of the concepts 'similar medicinal product' and 'clinical superiority' (OJ L 103, 28.4.2000, p. 5).

LEGISLATIVE FINANCIAL STATEMENT

1. FRAMEWORK OF THE PROPOSAL/INITIATIVE

1.1. Title of the proposal/initiative

1.2. Policy area(s) concerned

1.3. The proposal/initiative relates to:

1.4. Objective(s)

1.4.1. General objective(s)

1.4.2. Specific objective(s)

1.4.3. Expected result(s) and impact

1.4.4. Indicators of performance

1.5. Grounds for the proposal/initiative

1.5.1. Requirement(s) to be met in the short or long term including a detailed timeline for roll-out of the implementation of the initiative

1.5.2. Added value of Union involvement (it may result from different factors, e.g. coordination gains, legal certainty, greater effectiveness or complementarities). For the purposes of this point 'added value of Union involvement' is the value resulting from Union intervention which is additional to the value that would have been otherwise created by Member States alone.

1.5.3. Lessons learned from similar experiences in the past

1.5.4. Compatibility with the Multiannual Financial Framework and possible synergies with other appropriate instruments

1.5.5. Assessment of the different available financing options, including scope for redeployment

1.6. Duration and financial impact of the proposal/initiative

1.7. Management mode(s) planned

2. MANAGEMENT MEASURES

2.1. Monitoring and reporting rules

2.2. Management and control system(s)

2.2.1. Justification of the management mode(s), the funding implementation mechanism(s), the payment modalities and the control strategy proposed

2.2.2. Information concerning the risks identified and the internal control system(s) set up to mitigate them

2.2.3. Estimation and justification of the cost-effectiveness of the controls (ratio of "control costs ÷ value of the related funds managed"), and assessment of the expected levels of risk of error (at payment & at closure)

2.3. Measures to prevent fraud and irregularities

3. ESTIMATED FINANCIAL IMPACT OF THE PROPOSAL/INITIATIVE

3.1. Heading(s) of the multiannual financial framework and expenditure budget line(s) affected

3.2. Estimated financial impact of the proposal on appropriations

3.2.1. Summary of estimated impact on operational appropriations

3.2.2. Estimated output funded with operational appropriations

3.2.3. Summary of estimated impact on administrative appropriations

3.2.4. Compatibility with the current multiannual financial framework

3.2.5. Third-party contributions

3.3. Estimated impact on revenue

LEGISLATIVE FINANCIAL STATEMENT

1. FRAMEWORK OF THE PROPOSAL/INITIATIVE

1.1. Title of the proposal/initiative

Proposal for a revision of

Regulation (EC) No 726/2004 of the European Parliament and of the Council laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing a European Medicines Agency and

Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use and

Regulation (EC) No 141/2000 of the European Parliament and of the Council on orphan medicinal products and

Regulation (EC) No 1901/2006 of the European Parliament and of the Council on medicinal products for paediatric use[1].

1.2. Policy area(s) concerned

Heading 2: Cohesion, Resilience and Values

Activity: Health

1.3. The proposal/initiative relates to:

☐ **a new action**

☐ **a new action following a pilot project/preparatory action**[2]

X the extension of an existing action

X a merger or redirection of one or more actions towards another/a new action

[1] Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 (OJ L 378, 27.12.2006, p. 1).

[2] As referred to in Article 58(2)**, point** (a) or (b)**,** of the Financial Regulation.

1.4. Objective(s)

1.4.1. General objective(s)

The general objective of the revision is to guarantee a high level of public health by ensuring the quality, safety and efficacy of medicines for EU patients and harmonise the internal market.

1.4.2. Specific objective(s)

Specific objectives

1. Promote innovation, in particular for unmet medical needs, including for rare disease patients and children.

2. Create a balanced system for pharmaceuticals in the EU that promotes affordability for health systems while rewarding innovation.

3. Ensure access to innovative and established medicines for patients, with special attention to enhancing security of the supply across the EU.

4. Reduce the environmental impact of the pharmaceutical product life cycle.

5. Reduce the regulatory burden and provide a flexible regulatory framework.

1.4.3. Expected result(s) and impact

Specify the effects which the proposal/initiative should have on the beneficiaries/groups targeted.

The initiative builds on the high level of public health protection and harmonisation achieved for the authorisation of medicines, so that patients across the EU have timely and equitable access and a reliable supply of the medicines they need. Additional obligations and incentives should ensure that patients with rare diseases and children have access to high quality medicines and to safe and effective therapies to address their specific medical needs.

The sector's global competitiveness and innovative power should be supported by striking a balance between giving incentives for innovation, including for unmet medical needs, and measures on access and affordability,. as well as simplification and future-proofing through a framework that is adaptable to scientific and technological change and environmentally sustainable.

1.4.4. Indicators of performance

Specify the indicators for monitoring progress and achievements.

The following core indicators will generate information in a continuous and systematic way on implementation and performance.

For promoting innovation to address unmet medical needs:

– Number of authorised medicines addressing unmet medical needs or high unmet medical needs.

– Number of authorised novel antibiotics

For improving access to patients:

– Average time from authorisation to market launch for newly authorised medicines

– Number of member states in which new medicines launched within 2 years from authorisation

– Number of medicine shortages reported by member states

For environmental impact:

– Presence of medicines residues in the environment

For a flexible and attractive regulatory system:

– Number of authorised medicines with new active substance

– Average assessment time of newly authorised innovative medicines

1.5. Grounds for the proposal/initiative

1.5.1. Requirement(s) to be met in the short or long term including a detailed timeline for roll-out of the implementation of the initiative

Upon the entry into force of the Regulation, the Agency should put in place the framework which will be used to enhance regulatory support and accelerated assessment, to address medicine shortages and supply chain challenges and to strengthen the environmental risk assessment under the marketing authorisation.

Regarding the enhanced regulatory support, the Agency shall set up within 6 months of adoption a coordination mechanism to enable parallel scientific advice with health technology assessment and regulatory bodies for medical devices. Within the same period, the Agency shall create an Academia Office, a secretariat to support not-for-profit entities by providing them free of charge early scientific advice. Furthermore, the Agency shall establish an EU inspectorate within the Agency, to strengthen the network's inspection capacity and deal with emergencies, similar what was needed during the pandemic.

For addressing medicine shortages the Agency shall extend the monitoring and management capacity for all shortages, with a focus on critical shortages, and extend the EMA capacity to support availability of critical medicinal products. This would facilitate appropriate availability and access to medicinal products which may have a serious impact on public health.

The Agency shall also extend its capacity to support the enhanced environmental risk assessments.

1.5.2. Added value of Union involvement (it may result from different factors, e.g. coordination gains, legal certainty, greater effectiveness or complementarities). For the purposes of this point 'added value of Union involvement' is the value resulting from Union intervention which is additional to the value that would have been otherwise created by Member States alone.

Reasons for action at European level (ex-ante): Ensuring access to medicines is a clear public health interest in the EU. The current level of harmonisation shows that the authorisation of medicines can be effectively regulated at EU level. Uncoordinated measures by Member States may result in distortions of competition and barriers to intra-Union trade for products that are relevant for the entire EU. The initiative respects national exclusive competence in health services and pricing and reimbursement of medicines.

Expected generated Union added value (ex-post)

Currently there is no Union intervention to increase patient access to newly authorised medicines, and there is a significant variation between Member States in terms of access, especially the smaller markets are disadvantaged. The Union intervention will rely on the combined EU market power in encouraging companies to serve all Member States and in a timely fashion.

Most authorised innovative medicines are authorised through the centralised procedure, at EU level. Therefore, enhancing regulatory support is not only more effective at EU-level than at Member State level but also probably the only feasible option.

A coordinated response at Union-level to monitoring and mitigating the risk of shortages can help to avoid actions such as uncoordinated stockpiling being taken and therefore have both a positive impact on public health and maintain the smooth functioning of the single market.

Environmental hazards know no borders, therefore only an EU-level coordinated and standardised mitigation of environmental risks stemming from pharmaceuticals manufacturing, use and disposal can be effective.

1.5.3. Lessons learned from similar experiences in the past

The EU pharmaceutical legislation roots back to 1961, the first common EU rules for authorisation. Much of the impetus behind the adoption of the legal framework stemmed from the determination to prevent a recurrence of the thalidomide disaster of the late 1950s, when thousands of babies were born with limb deformities as a result of their mothers taking a medicinal product during pregnancy. This experience, which shook public health authorities and the general public, made it clear that to safeguard public health, no medicinal product must ever again be marketed without prior authorisation.

Since then, a large body of legislation has been developed around this principle, with the progressive harmonisation of requirements for the granting of marketing authorisation, and post-marketing monitoring, implemented across the entire European Economic Area (EEA).

Beyond safety, and harmonised rules for medicinal products to enable a single market, incentives have been introduced to support innovation. Dedicated incentives for medicines for rare diseases and medicines for children have boosted research and innovation in these areas, leading to scientific breakthroughs and life-saving new products.

Both the obligations and incentives have proven to be largely effective, and the lessons learned from their application drove the current revision. Revision and modulation of existing obligations and incentives and adding new ones will serve new and recurring goals:

– Promoting innovation and addressing unmet medical needs

– Promoting access to affordable medicines

– Enhancing security of supply of medicines

– Reducing the environmental impact of medicines

– Reducing regulatory burden and providing a flexible and future-proof regulatory framework

1.5.4. Compatibility with the Multiannual Financial Framework and possible synergies with other appropriate instruments

The Agency should cooperate and promote synergies with other Union bodies, such as the European Centre for Disease and Control (ECDC), European Food Safety Authority (EFSA) and take full advantage and ensure consistency with the EU4Health programme and other EU programmes financing actions in the domain of public health.

1.5.5. Assessment of the different available financing options, including scope for redeployment

The overall budgetary impact of the revision to the Pharma legislation is 17.8 million EUR for the period 2024-2027 (excluding the costs for fee-financed staff). This amount will cover the development and the maintenance of the data register from Environmental Risk Assessment studies; activities related to shortage management and security of supply; the development of a new IT module for third-country inspections of decentralised manufacturing, development and maintenance of the union register of orphan designations and the support to “not-for-profit” entities. Most of these budgetary needs will be covered by EMA fees therefore the impact on the EU budget amounts to 4.4 million EUR. The 4.4 million EUR that will result in an increase of the EMA annual subsidy for the current MFF period will be redeployed internally within Heading 2b, by a corresponding reduction of the EU4Health programme’s budgetary envelope in years 2026 and 2027.

1.6. Duration and financial impact of the proposal/initiative

☐ **limited duration**

– ☐ in effect from [DD/MM]YYYY to [DD/MM]YYYY

– ☐ Financial impact from YYYY to YYYY for commitment appropriations and from YYYY to YYYY for payment appropriations.

☑ **unlimited duration**

– Implementation with a start-up period from 2023 to 2024,

– followed by full-scale operation.

1.7. Management mode(s) planned[3]

☑ **Direct management** by the Commission

– ☐ by its departments, including by its staff in the Union delegations;

– ☐ by the executive agencies

☐ **Shared management** with the Member States

☑ **Indirect management** by entrusting budget implementation tasks to:

– ☐ third countries or the bodies they have designated;

– ☐ international organisations and their agencies (to be specified);

– ☐ the EIB and the European Investment Fund;

– ☑ bodies referred to in Articles 70 and 71 of the Financial Regulation;

– ☐ public law bodies;

– ☐ bodies governed by private law with a public service mission to the extent that they provide adequate financial guarantees;

– ☐ bodies governed by the private law of a Member State that are entrusted with the implementation of a public-private partnership and that provide adequate financial guarantees;

[3] Details of management modes and references to the Financial Regulation may be found on the BudgWeb site: https://myintracomm.ec.europa.eu/budgweb/EN/man/budgmanag/Pages/budgmanag.aspx

– ☐ persons entrusted with the implementation of specific actions in the CFSP pursuant to Title V of the TEU, and identified in the relevant basic act.

– *If more than one management mode is indicated, please provide details in the 'Comments' section.*

Comments

2. MANAGEMENT MEASURES

2.1. Monitoring and reporting rules

Specify frequency and conditions.

All Union agencies work under a strict monitoring system involving an internal control coordinator, the Internal Audit Service of the Commission, the Management Board, the Commission, the Court of Auditors and the Budgetary Authority. This system is reflected and laid down in the EMA's founding regulation. In accordance with the Joint Statement on the EU decentralised agencies (the 'Common Approach'), the framework financial regulation (2019/715) and related Commission Communication C(2020)2297, the annual work programme and Single Programming Document of the Agency comprise detailed objectives and expected results, including a set of performance indicators. The Single Programming Document combines multiannual and annual programming as well as "strategy documents", e.g. on independence. DG SANTE comments through the Agency's Management Board and prepares a formal Commission Opinion on the Single Programming Document. The activities of the Agency will be measured against these indicators in the Consolidated Annual Activity Report. The Agency will monitor periodically the performance of its internal control system to ensure that data is collected efficiently, effectively and timely and to identify internal control deficiencies, register and assess the results of controls, control deviations and exceptions. The results of the internal control assessments, including significant weaknesses identified and any differences as compared to internal and external audit findings will be disclosed in the Consolidated Annual Activity report.

2.2. Management and control system(s)

2.2.1. Justification of the management mode(s), the funding implementation mechanism(s), the payment modalities and the control strategy proposed

The annual EU subsidy will be transferred to the Agency in accordance with its payment needs and upon its request. The Agency will be subject to administrative controls including budgetary control, internal audit, annual reports by the European Court of Auditors, the annual discharge for the execution of the EU budget and possible investigations conducted by OLAF to ensure, in particular, that the resources allocated to the Agency are put to proper use. Through its representation in the Agency's Management Board and Audit Committee, the Commission will receive audit reports and ensures that adequate actions are defined and timely implemented by the Agency to address the issues identified. All payments will remain pre-financing payments until the Agency's accounts have been audited by the European Court of Auditors and the Agency has submitted its final accounts. If necessary, the Commission will recover unspent amounts of the instalments paid to the Agency.

The activities of the Agency will also be subject to the supervision of the Ombudsman in accordance with Article 228 of the Treaty. These administrative controls provide a number of procedural safeguards to ensure that account is taken of the interests of the stakeholders.

2.2.2. Information concerning the risks identified and the internal control system(s) set up to mitigate them

The main risks relate to the Agency's performance and independence in implementing the tasks entrusted to it. Underperformance or impaired independence could hamper the achievement of the objectives of this initiative and also reflect negatively on the Commission's reputation.

The Commission and the Agency have put in place internal procedures that aim at covering the risks identified above. The internal procedures are in full compliance with the Financial Regulation and include anti-fraud measures and cost-benefit considerations.

First and foremost, sufficient resources should be made available to the Agency in both financial and staffing terms to achieve the objectives of this initiative.

Furthermore, quality management will include both the integrated quality-management activities and risk-management activities within the Agency. A risk review is conducted annually, with risks being assessed at a residual level, i.e. taking into account controls and mitigations already in place. Conducting self-assessments (as part of the EU Agencies benchmarking programme), annual reviews of sensitive functions and ex-post controls also fall within this area, as does maintain a register of exceptions.

To preserve impartiality and objectivity in every aspect of the Agency's work, a number of policies and rules on management of competing interests have been put in place and will be regularly updated, describing specific arrangements, requirements and processes

applying to the Agency's Management Board, scientific committee members and experts, the Agency's staff and candidates, as well as consultants and contractors.

The Commission will be informed timely of relevant management and independence issues encountered by the Agency and will react upon notified issues timely and adequately.

2.2.3. Estimation and justification of the cost-effectiveness of the controls (ratio of "control costs ÷ value of the related funds managed"), and assessment of the expected levels of risk of error (at payment & at closure)

The Commission's and the Agency's internal control strategies take into consideration the main cost drivers, and the efforts already taken over several years to reduce the cost of controls, without compromising the effectiveness of controls. The existing control systems proved to be able to prevent and/or to detect errors and/or irregularities, and in case of errors or irregularities, to correct them.

In the past five years, the Commission's yearly costs of controls under indirect management represented less than 1% of the annual budget spent on subsidies paid to the Agency. The Agency allocated less than 0,5% of its total annual budget on control activities centering around integrated quality management, audit, anti-fraud measures, finance and verification processes, corporate risk management and self-assessment activities.

2.3. Measures to prevent fraud and irregularities

Specify existing or envisaged prevention and protection measures, e.g. from the Anti-Fraud Strategy.

As for its activities in indirect management, the Commission shall take appropriate measures ensuring that the financial interests of the European Union are protected by the application of preventive measures against fraud, corruption and any other illegal activities, by effective checks and, if irregularities are detected, by the recovery of the amounts wrongly paid and, where appropriate, by effective, proportional and deterrent penalties.

To this effect, the Commission adopted an anti-fraud strategy, latest update of April 2019 (COM(2019)176), covering preventive, detective and corrective measures.

The Commission or its representatives and the European Court of Auditors shall have the power of audit, on the basis of documents and on-the-spot, over all grant beneficiaries, contractors and subcontractors who have received Union funds. OLAF shall be authorised to carry out on-the-spot checks and inspections on economic operators concerned indirectly by such funding.

As regards the European Medicines Agency, the anti-fraud measures are provided for in Article 69 of Regulation (EC) No 726/2004 and the framework financial Regulation (2019/715). The Executive Director and the Management Board of the Agency will take the appropriate measures in accordance with the Internal Control Principles applied across all EU institutions. In line with the Common

Approach and Article 42 of the framework financial Regulation, an anti-fraud strategy has been developed and is followed by the Agency.

The Agency's Anti-fraud strategy covers 3-year period and is accompanied by a corresponding action plan, outlining both specific focus areas and actions for the next years, and several continuous actions that are carried out every year, such as a specific standalone fraud risk assessment, with the identified fraud risks included in the overall Agency risk register. Anti-fraud trainings are organised as part of the induction training and via mandatory anti-fraud e-learning training for newcomers. Staff are made aware of how to report any suspects of wrongdoings and disciplinary procedures are in place as per the rules of the Staff Regulations.

3. ESTIMATED FINANCIAL IMPACT OF THE PROPOSAL/INITIATIVE

3.1. Heading(s) of the multiannual financial framework and expenditure budget line(s) affected

- Existing budget lines

In order of multiannual financial framework headings and budget lines.

Heading of multiannual financial framework	Budget line	Type of expenditure	Contribution			
	Number	Diff./Non-diff.[4]	from EFTA countries[5]	from candidate countries[6]	from third countries	within the meaning of Article 21(2)(b) of the Financial Regulation
2	06.100302 Special contribution for orphan medicinal products	Non-diff.	YES	NO	NO	NO

3.2. Estimated financial impact of the proposal/initiative

3.2.1. Summary of estimated impact on operational appropriations

– ☐The proposal/initiative does not require the use of operational appropriations

– ☑The proposal/initiative requires the use of operational appropriations, as explained below:

EUR million (to three decimal places)

Heading of multiannual financial framework	2	Cohesion, Resilience and Values

[4] Diff. = Differentiated appropriations / Non-diff. = Non-differentiated appropriations.
[5] EFTA: European Free Trade Association.
[6] Candidate countries and, where applicable, potential candidates.

DG: SANTE			Year **2024**	Year **2025**	Year **2026**	Year **2027 and subsequent years**	**TOTAL**[7]
• Operational appropriations							
06.100302 Special contribution for orphan medicinal products	Commitments	(1b)			1.172	3.196	4.368
	Payments	(2b)			1.172	3.196	4.368
Appropriations of an administrative nature financed from the envelope of specific programmes[8]							
Budget line		(3)					
TOTAL appropriations for DG SANTE	Commitments	=1a+1b +3			1.172	3.196	4.368
	Payments	=2a+2b +3			1.172	3.196	4.368

• TOTAL operational appropriations	Commitments	(4)			1.172	3.196	4.368
	Payments	(5)			1.172	3.196	4.368
• TOTAL appropriations of an administrative nature financed from the envelope for specific programmes		(6)					
TOTAL appropriations under HEADING <2b>	Commitments	=4+ 6			1.172	3.196	4.368
	Payments	=5+ 6			1.172	3.196	4.368

7 For 2026 the total amount covers the costs for 6 TAs. For 2027 the total amount covers the costs for 6 TAs (1.196 million EUR) and the costs for the incentives to "not-for-profit" entities (2 million EUR).

8 Technical and/or administrative assistance and expenditure in support of the implementation of EU programmes and/or actions (former 'BA' lines), indirect research, direct research.

of the multiannual financial framework							

Heading of multiannual financial framework	7	'Administrative expenditure'

This section should be filled in using the 'budget data of an administrative nature' to be firstly introduced in the Annex to the Legislative Financial Statement (Annex V to the internal rules), which is uploaded to DECIDE for interservice consultation purposes.

EUR million (to three decimal places)

		Year **2024**	Year **2025**	Year **2026**	Year **2027 and subsequent years**	Enter as many years as necessary to show the duration of the impact (see point 1.6)			**TOTAL**
DG: SANTE									
• Human resources									
• Other administrative expenditure									
TOTAL DG <…….>	Appropriations								

TOTAL appropriations under HEADING 7 of the multiannual financial framework	(Total commitments = Total payments)								

EUR million (to three decimal places)

		Year **2024**	Year **2025**	Year **2026**	Year **2027**	Enter as many years as necessary to show the duration of the impact (see point 1.6)			**TOTAL**
TOTAL appropriations under HEADINGS 1 to 7 of the multiannual financial framework	Commitments			1.172	3.196				4.368
	Payments			1.172	3.196				4.368

3.2.2. Estimated output funded with operational appropriations

Commitment appropriations in EUR million (to three decimal places)

Indicate objectives and outputs ⇩			Year **2024**		Year **2025**		Year **2026**		Year **2027 and subsequent years**		**TOTAL**	
	OUTPUTS											
	Type[9]	Average cost	No	Cost	No	Cost	No	Cost	No	Cost	Total No	Total cost
Specific objective 1. Promote innovation, in particular for unmet medical needs, including for rare disease patients and children.												
Support to "not-for-profit" entities								1.172		3.196		4.368
Subtotal for specific objective No 1								1.172		3.196		4.368
TOTALS								1.172		3.196		4.368
- Output												

[9] Outputs are products and services to be supplied (e.g.: number of student exchanges financed, number of km of roads built, etc.).

3.2.3. Estimated impact on EMA's human resources

– ☐ The proposal/initiative does not require the use of appropriations of an administrative nature

– ☐ The proposal/initiative requires the use of appropriations of an administrative nature, as explained below:

EUR million (to three decimal places)

	Year **2024**	Year **2025**	Year **2026**	Year **2027 and subsequent years**	**TOTAL**
Temporary agents (AD Grades)			0.781	0.797	1.578
Temporary agents (AST grades)			0.391	0.399	0.790
Contract staff					
Seconded National Experts					
TOTAL			**1.172**	**1.196**	**2.368**

Staff requirements (FTE): Total posts Union funded and funded from fees

	Year **2024**	Year **2025**	Year **2026**	Year **2027 and subsequent years**	**TOTAL**
Temporary agents (AD Grades)	13	22	33	40	40
Temporary agents (AST grades)	6	15	19	20	20
Contract staff					
Seconded National Experts					

TOTAL	**19**	**37**	**52**	**60**	**60**

The appropriations required for human resources and other expenditure of an administrative nature will be met by appropriations from the DG that are already assigned to management of the action and/or have been redeployed within the DG, together if necessary with any additional allocation which may be granted to the managing DG under the annual allocation procedure and in the light of budgetary constraints.

3.2.3.1. Estimated requirements of human resources

– ☐ The proposal/initiative does not require the use of human resources.

– ☐ The proposal/initiative requires the use of human resources, as explained below:

Estimate to be expressed in full time equivalent units

		Year **2024**	Year **2025**	Year **2026**	Year **N+3**	Enter as many years as necessary to show the duration of the impact (see point 1.6)		
• Establishment plan posts (officials and temporary staff)								
20 01 02 01 (Headquarters and Commission's Representation Offices)								
20 01 02 03 (Delegations)								
01 01 01 01 (Indirect research)								
01 01 01 11 (Direct research)								
Other budget lines (specify)								
• External staff (in Full Time Equivalent unit: FTE)[103]								
20 02 01 (AC, END, INT from the 'global envelope')								
20 02 03 (AC, AL, END, INT and JPD in the delegations)								
XX 01 xx **yy zz** [104]	- at Headquarters							
	- in Delegations							
01 01 01 02 (AC, END, INT - Indirect research)								
01 01 01 12 (AC, END, INT - Direct research)								
Other budget lines (specify)								
TOTAL								

XX is the policy area or budget title concerned.

The human resources required will be met by staff from the DG who are already assigned to management of the action and/or have been redeployed within the DG, together if necessary with any additional allocation which may be granted to the managing DG under the annual allocation procedure and in the light of budgetary constraints.

Description of tasks to be carried out from the FTE, funded by Union contribution:

Officials and temporary staff	The requested FTE (4 AD and 2 AST) are necessary to set up the Academia Office at EMA that will be managing the procedures. The tasks of the office will be similar to the tasks of the SME office and will include procedural and administrative assistance to "not-for-profit" entities, including direct assistance and briefing meetings on regulatory strategy, providing fee waivers and reductions to eligible entities, provide free-of-charge translations of the product information in all EU languages for initial EU marketing authorisations, provide training and education to "not-for-profit" entities, etc
External staff	

[103] AC= Contract Staff; AL = Local Staff; END= Seconded National Expert; INT = agency staff; JPD= Junior Professionals in Delegations.

[104] Sub-ceiling for external staff covered by operational appropriations (former 'BA' lines).

3.2.4. Description of tasks to be carried out from the FTE, funded by EMA fees:

Officials and temporary staff	The requested staff (54 FTE) will be: • managing (AD profiles) and providing support (AST profiles) to operational expert groups in the area of the Environmental Risk Assessment (ERA); • with a scientific and regulatory profile to work in the shortages management and security of supply; • Good Manufacturing Practice and Good Clinical Practice inspectors (AD) necessary to establish an EU inspectorate resourced by EMA staff that would provide help to the inspections done by Member States (lacking resources), and deal with emergency situations which require dedicated and dependable intervention (e.g., similar to inspections required during the pandemic); • Legal officers (AD profiles), needed in the field of orphan designations that are already today a litigious topic and so it is assumed the proposed changes in the decision making on orphan designation would generate an increased in workload for even more legal queries and litigations; • defining business requirements for the data register, following up on the implementation and perform the related scientific activities when the register is live;, develop trainings on ERA, etc.; • providing administrative support to the operational expert groups; • working in the area of inspection planning; • general assistants, assistants, supporting on procedural aspects or working on document creation.
External staff	

3.2.5. Compatibility with the current multiannual financial framework

The proposal/initiative:

– ☑ can be fully financed through redeployment within the relevant heading of the Multiannual Financial Framework (MFF).

The increase of appropriations for EMA budget line 06.100302 in years 2026 and 2027 by 4.4 million EUR, will be done via internal redeployment within heading 2b, i.e. by an equal reduction of the EU4Health budget line 06.0601 for this period.

– ☐ requires use of the unallocated margin under the relevant heading of the MFF and/or use of the special instruments as defined in the MFF Regulation.

Explain what is required, specifying the headings and budget lines concerned, the corresponding amounts, and the instruments proposed to be used.

– ☐ requires a revision of the MFF.

Explain what is required, specifying the headings and budget lines concerned and the corresponding amounts.

3.2.6. Third-party contributions

The proposal/initiative:

– ☑ does not provide for co-financing by third parties

– ☐ provides for the co-financing by third parties estimated below:

Appropriations in EUR million (to three decimal places)

	Year **2024**	Year **2025**	Year **2026**	Year **2027 and subsequent years**	Enter as many years as necessary to show the duration of the impact (see point 1.6)			Total
Specify the co-financing body								
TOTAL appropriations co-financed								

3.3. Estimated impact on revenue

– ☑ The proposal/initiative has no financial impact on revenue.

– ☐ The proposal/initiative has the following financial impact:

  – ☐ on own resources

  – ☐ on other revenue

  – please indicate, if the revenue is assigned to expenditure lines ☐

EUR million (to three decimal places)

Budget revenue line:	Appropriations available for the current financial year	Impact of the proposal/initiative[105]						
		Year **2024**	Year **2025**	Year **2026**	Year **2027 and subsequent years**	Enter as many years as necessary to show the duration of the impact (see point 1.6)		
Article …….								

For assigned revenue, specify the budget expenditure line(s) affected.

Other remarks (e.g. method/formula used for calculating the impact on revenue or any other information).

[105] As regards traditional own resources (customs duties, sugar levies), the amounts indicated must be net amounts, i.e. gross amounts after deduction of 20 % for collection costs.

EUROPEAN
COMMISSION

Brussels, 26.4.2023
SWD(2023) 192 final

PART 1/2

COMMISSION STAFF WORKING DOCUMENT

IMPACT ASSESSMENT REPORT

Accompanying the documents

Proposal for a Directive of the European Parliament and of the Council on the Union code relating to medicinal products for human use, and repealing Directive 2001/83/EC and Directive 2009/35/EC

Proposal for a Regulation of the European Parliament and of the Council laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, amending Regulation (EC) No 1394/2007 and Regulation (EU) No 536/2014 and repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006

{COM(2023) 192 final} - {COM(2023) 193 final} - {SEC(2023) 390 final} -
{SWD(2023) 191 final} - {SWD(2023) 193 final}

GLOSSARY

Term or acronym	*Meaning or definition*
Accessibility	A medicine becomes accessible to patients once it has been authorised, is being marketed, and can be reimbursed in a Member State.
Affordability	Relates to payments to be made by patients (out of pocket on healthcare or through co-payments) which can be described as affordability at micro level and to the sustainability of public funding of the healthcare sector raised through social security contributions or taxes (affordability at macro level).
AMR	Antimicrobial resistance.
Antibacterial/antibiotic	Any substance with a direct action on bacteria that is used for treatment or prevention of infections or infectious diseases.
Antimicrobial	Any substance with a direct action on micro-organisms used for treatment or prevention of infections or infectious diseases, including antibiotics, antivirals, antifungals and anti-protozoals.
Antimicrobial resistance (AMR)	The ability of micro-organisms to survive or to grow in the presence of a concentration of an antimicrobial agent which is usually sufficient to inhibit or kill micro-organisms of the same species.
API	Active Pharmaceutical Ingredient.
ATC	Anatomical Therapeutic Chemical code.
Conditional marketing authorisation	Conditional marketing authorisation is the approval to market a medicine that addresses patients' unmet medical needs on the basis of data that is less comprehensive than that normally required. The available data must indicate that the medicine's benefits outweigh its risks and the applicant should be in a position to provide comprehensive clinical data in the future.

CMDh	The Coordination Group for Mutual recognition and Decentralised Procedures – Human is EMA's committee responsible for the examination and coordination of questions relating to the marketing authorisation of human medicines in two or more Member States in accordance with the mutual recognition or decentralised procedure.
COM	European Commission.
COMP	The Committee for Orphan Medicinal Products is the Agency's committee responsible for recommending orphan designation of medicines for rare diseases.
CP	The centralised authorisation procedure is the European Union-wide procedure for the authorisation of medicines, where there is a single application, a single evaluation and a single authorisation granted by the European Commission valid throughout the EU.
Data protection	Period of protection during which pre-clinical and clinical data and data from clinical trials handed in to the authorities by one company cannot be referenced by another company in their regulatory filings.
DCP	The decentralised procedure is the procedure for authorising medicines in more than one European Union Member State in parallel. It can be used for medicines that do not need to be authorised via the centralised procedure and have not already been authorised in any Member State. The DCP was introduced by Directive 2004/27/EC, by the 2004 revision.
EEA	The European Economic Area includes all EU Member States and also Iceland, Liechtenstein and Norway.
EMA	The European Medicines Agency ('the Agency') is an EU agency founded in 1995 which is responsible for the scientific evaluation, supervision and safety monitoring of medicines, both human and veterinary, across the EU.
ERA	Environmental Risk Assessment
EU	European Union.
EudraVigilance	A centralised European database of suspected adverse

	reactions to medicines that are authorised or being studied in clinical trials in the European Economic Area (EEA).
Evergreening	'Evergreening' strategies extend the effective patent period and thus allow drug companies to maintain a market share after their drug patents expire by introducing "follow-on drugs" – those with slight changes made to them after expired patents allow generic competitors to enter the market.
FDA	United States Food and Drug Administration.
GDP	Good Distribution Practices.
GDPR	General Data Protection Regulation.
GMP	Good Manufacturing Practices.
GMO	Genetically Modified Organism.
Generic medicine	A generic medicine contains the same active substance(s) as the reference medicine, and it is used at the same dose(s) to treat the same disease(s). The generic can only be marketed after expiry of the data and market protection of its reference medicine.
HTA	Health Technology Assessment is a multidisciplinary process that summarises information about the medical, patient and social aspects and the economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased and robust manner.
HUMN	High Unmet Medical Need
IA	An impact assessment identifies and describes the problems to be tackled, establishes objectives, formulates policy options, assesses the impacts of these options and describes how the expected results will be monitored. The Commission's impact assessment system follows an integrated approach that assesses the environmental, social and economic impacts of a range of policy options.
ICER	An incremental cost-effectiveness ratio is a summary measure representing the economic value of an intervention, compared with an alternative (the comparator). An ICER is calculated by dividing the difference in total costs (incremental cost) by the difference in the chosen measure of health outcome or effect (incremental effect) to provide a ratio of 'extra cost per extra unit of health effect' for the more

	expensive therapy versus the alternative.
IP	Intellectual property
IQVIA	IQVIA is a contract research and analytical services organisation that collects data including global pharmaceutical sales data.
Killer acquisitions	'Killer acquisitions' is used as shorthand for: 'acquisitions' (in a wide economic sense) of innovative competitors which have as their object or effect the discontinuation of overlapping R&D projects to the detriment of innovation competition and ultimately consumers. Cunningham, C., Ederer, F. and Ma, S. (2021), "Killer acquisitions", Journal of Political Economy, Vol. 129, No. 3, pp. 649–702. 2
MA	A marketing authorisation is the mandatory approval process before a medicine enters the market of one, several or all EU Member States.
MAH	Marketing authorisation holder
Marketing authorisation application	An application made to a European regulatory authority for approval to market a medicine within the EU.
Marketing authorisation grant	A decision granting the marketing authorisation issued by the relevant authority.
Market exclusivity	The period after the marketing authorisation of a medicine for a rare disease when similar medicines for the same indication cannot be placed on the market and applications for those medicines cannot be validated. Under the current legislation, the market exclusivity has a duration of 10 years.
Market protection	Period of protection during which generics cannot be placed on the market.
MDGs	The United Nations Millennium Development Goals are 8 goals that UN Member States have agreed to try to achieve by the year 2015 to reduce extreme poverty. The MDGs have been superseded by the United Nations Sustainable Development Goals.
Medical condition	Any deviation(s) from the normal structure or function of the body, as manifested by a characteristic set of signs and symptoms (typically a recognised distinct disease or a syndrome).
Megatrend	Megatrends are long-term driving forces that are observable now and will most likely have significant

	influence on the future. Megatrends are closely interlinked between each other and simultaneously affect many different stakeholders. Thus, a systemic and global understanding of the issue under study is necessary to fully picture and illustrate the dynamics at stake. See also: The Megatrends Hub | Knowledge for policy (europa.eu)
MRP	The mutual recognition procedure (MRP) is a procedure through which an authorisation of a medicine in one EU Member State is recognised by another Member State.
MS	Member States are countries member of the EU.
National authorisation procedure	The national authorisation procedure is a marketing authorisation procedure where individual Member States authorise medicines for use in their own territory. This procedure depends on national legislation.
NAS	New active substances.
NCA	National Competent Authority.
NCE	New Chemical Entity.
"Off-label" use	Use of a medicine for an unapproved indication or in an unapproved age group, dosage, or route of administration.
Oncology	A branch of medicine that specialises in the prevention, diagnosis and treatment of cancer.
Orphan designation	A status assigned to a medicine intended for use against a rare condition. The medicine must fulfil certain criteria for designation so that it can benefit from incentives such as market exclusivity.
Parallel import	Parallel import/trade is based on the principle of free movement of goods in the internal market (TFEU Articles 34 and 36). This trade is known as "parallel" to the extent that it takes place outside and – in most cases – in parallel with the distribution network that the manufacturers or original suppliers have established for their products.
Payer	An entity responsible for financing or reimbursing healthcare.

PDCO	The Paediatric Committee is EMA scientific committee responsible for activities associated with medicines for children. It supports the development of such medicines in the EU by providing scientific expertise and defining paediatric need.
Personalised medicine	A medical model using characterisation of individuals' phenotypes and genotypes (e.g. molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention.
Pharmacovigilance	The monitoring of the safety of an authorised medicine and the detection of any change to its benefit-risk balance.
PIP	A paediatric investigation plan is a development plan designed to ensure that the data required to support the authorisation of a paediatric medicine are obtained through studies of its effect on children.
PRIME	The priority medicine scheme has been launched by the European Medicines Agency to enhance support for the development of medicines that target an unmet medical need. Through this voluntary scheme the Agency offers early and proactive support to medicine developers to optimise the generation of robust data on a medicine's benefits and risks, to optimise development plans and to enable accelerated assessment of applications.
QALYs	Quality-adjusted life years refers to a measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to one year of life in perfect health. QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality-of-life score (on a 0 to 1 scale). It is often measured in terms of the person's ability to carry out the activities of daily life and freedom from pain and mental disturbance.
Rare disease	Diseases with a particularly low prevalence. The EU considers diseases to be rare when they affect no more than 5 per 10,000 people in the EU.
Repurposed medicines	Medicines repurposing identifies new uses for licensed medicines that are outside of the scope of the originally intended use for the medicine. This typically involves taking an existing medicine that already has a marketing authorisation or licence for human use for a

	particular condition, and then using it to treat another condition. Alternatively, a repurposed medicine may be used in a different dose, or form, than its original licence (for example an inhaled product, rather than a tablet).
RSB	The Regulatory Scrutiny Board is an independent body of the Commission that offers advice to the College of Commissioners. It provides a central quality control and support function for the Commission's impact assessment and evaluation work. The Board examines and issues opinions and recommendations on all the Commission's draft impact assessments and its major evaluations and fitness checks of existing legislation.
Repeat use procedure (RUP)	Repeat Use Procedure is the use of the Mutual Recognition Procedure (MRP) after the completion of a first MRP or Decentralised Procedure (DCP) for the recognition of a marketing authorisation by other Member States.
SA	A scientific advice (SA) is the provision of advice by the Agency on the appropriate tests and studies required in developing a medicine, or on the quality of a medicine.
SDGs	The United Nations Sustainable Development Goals (UN SDGs) are 17 goals with 169 targets that all UN Member States have agreed to work towards achieving by the year 2030. They set out a vision for a world free from poverty, hunger and disease.
SmPC	A summary of product characteristics (SmPC) describes the properties and the officially approved conditions of use of a medicine.
SMEs	Micro, small and medium-sized enterprises.
SPC	The supplementary protection certificate is an intellectual property right that serves as an extension to a patent right. The patent right extension applies to specific pharmaceutical and plant protection products that have been authorised by regulatory authorities.
SWD	Staff working documents are required to present the results of all impact assessments and evaluations/fitness checks.
Therapeutic indication	The proposed indication for the marketing authorisation. A medical condition that a medicine is used for. This can include the treatment, prevention and diagnosis of a disease. The therapeutic indication

	granted at the time of marketing authorisation will be the result of the assessment of quality, safety and efficacy data submitted with the marketing application.
UMN	Unmet medical need - see Annex 6 for possible criteria for unmet medical need.

1 INTRODUCTION: POLITICAL AND LEGAL CONTEXT

This impact assessment covers Directive 2001/83/EC[1] and Regulation (EC) No 726/2004[2] ("general pharmaceutical legislation"). The EU general pharmaceutical legislation was established in 1965 with the dual objective of safeguarding public health and harmonising the internal market for medicines. It has developed considerably since then, but these overarching objectives have guided all revisions. The general pharmaceutical legislation is complemented by the *specialised* legislation for medicines for rare diseases ('Orphan Regulation')[3], medicines for children ('Paediatric Regulation')[4], currently under revision, and advanced therapy medicines ('ATMP Regulation')[5]. The general legislation applies to these specialised medicines, while the specialised frameworks provide additional measures to address their specific characteristics. In particular, they address market failures by providing specific *incentives* for development of medicines for small number of patients affected by rare diseases and *rewards* for companies that fulfil the *obligation* to screen adult medicines under development for use in children[6]. The ATMP regulation adapts the technical requirements for the authorisation of medicines based on genes, tissues or cells.

The general pharmaceutical legislation governs the granting of marketing authorisations for all medicines for human use by defining conditions and procedures to enter and remain on the market. A fundamental principle is that a marketing authorisation is granted only to medicines with a positive benefit-risk balance after assessment of their quality, safety and efficacy.

The most recent comprehensive revision took place in 2004 while targeted revisions on post-authorisation monitoring (pharmacovigilance)[7] and on falsified medicines[8] were adopted subsequently. In the almost 20 years since this revision, the pharmaceutical sector has changed and has become more globalised, both in terms of development and manufacture. The roles of 'big pharma' and SMEs have changed, with emerging biopharma companies – often SMEs – increasingly driving innovation and development, with these developments taken over by 'big pharma' through acquisitions or licence agreements.[9] Science and technology have evolved at a rapid pace. However, there continues to be unmet medical needs[10], i.e. diseases without or only with suboptimal treatments. Moreover, some patients may not benefit from innovation because medicines may be unaffordable or not launched (i.e. placed on the market) in the Member State concerned. There is

[1] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, OJ L 311, 28.11.2001, p.67.

[2] Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing a European Medicines Agency, OJ L136, 30.4.2004, p.1.

[3] Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products

[4] Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004

[5] Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004

[6] See Annex 6 for further details on the coherence between the two initiatives.

[7] Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use, OJ L 348, 31.12.2010, p. 74, and Directive 2012/26/EU of the European Parliament and of the Council of 25 October 2012 amending Directive 2001/83/EC as regards pharmacovigilance, OJ L 299, 27.10.2012, p. 1.

[8] Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of entry into the legal supply chain of falsified medicinal products, OJ L 174, 1.7.2011, p. 74.

[9] See Annex 9 for further description of the pharmaceutical ecosystem.

[10] Possible criteria to define unmet medical need are described in Annex 6.

also a greater awareness of the environmental impact of medicines. More recently, the COVID-19 pandemic has stress tested the framework.

This impact assessment (IA) analyses policy options designed to address shortcomings highlighted in the evaluation[11] of the general pharmaceutical legislation, taking into account the lessons learnt from the COVID-19 pandemic. It was conducted in parallel with the evaluation (a 'back-to-back' exercise).

The revision is part of the implementation of the Pharmaceutical strategy for Europe[12] and aims to:

- Promote innovation, in particular for unmet medical needs, while reducing regulatory burden and the environmental impact of medicines;
- Ensure access to innovative and established medicines for patients, with special attention to enhancing security of supply and addressing risks of shortages, taking into account the challenges of the smaller markets of the EU;
- Create a balanced and competitive system that keeps medicines affordable for health systems while rewarding innovation.

This revision focuses on provisions relevant to achieve its specific objectives; therefore it covers all but provisions concerning advertising, falsified medicines, homeopathic and traditional herbal medicines. The revision of the general pharmaceutical legislation will be presented as a 'package' with the revision of the orphan and paediatric legislation. The ATMP regulation is not revised, but the revision of the general legislation will address some of the issues, e.g. broad application of hospital exemption, innovative or specific manufacturing methods for these products and burdensome procedures, identified[13] through the experience accumulated since the entry into force of the ATMP Regulation and will help translate research into ATMPs available to patients across the EU while maintaining a high level of public health protection.

1.1 Political context

Since the 2004 revision of the general pharmaceutical legislation, certain aspects such as unequal patient access, affordability, shortages, or the environmental impact of medicines have become more prominent and moved up the political agenda. This is evidenced by recent Council conclusions[14] and resolutions of the European Parliament[15] which called for a balanced system of incentives, rewarding innovation while improving access. Member States called for revised mechanisms and incentives for medicines development tailored to the level of unmet medical need, while ensuring patient access and availability of medicines in all Member States. The COVID-19 pandemic has spotlighted some critical issues in the European pharmaceutical policy.

The Pharmaceutical strategy for Europe[16] – adopted in November 2020 – is an important building block of the European Health Union[17] and more than a response to the pandemic. The strategy is a holistic answer to the current challenges of the pharmaceutical policy with 55 legislative and non-

[11] Annex 5.
[12] COM(2020) 761 final.
[13] COM(2014) 188 final.
[14] Council conclusions on strengthening the balance in the pharmaceutical systems in the EU and its Member States, OJ C, C/269, 23.07.2016, p. 31. Strengthening the European Health Union: improving accessibility to and availability of medicinal products and medical devices. Council Conclusions on Access to medicines and medical devices for a Stronger and Resilient EU, (2021/C 269 I/02).
[15] European Parliament resolution of 2 March 2017 on EU options for improving access to medicine (2016/2057(INI)) Shortages of medicines, 2020/2071(INI).
[16] COM(2020) 761 final https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe_en
[17] COM(2020) 724 final, available at https://ec.europa.eu/info/strategy/priorities-2019-2024/promoting-our-european-way-life/european-health-union_en.

legislative actions interacting together to achieve its overall goal of ensuring Europe's supply of safe and affordable medicines and supporting the European pharmaceutical industry's innovation efforts[18]. The revision of the general pharmaceutical legislation and the ongoing revision of the legislation on medicines for children and rare diseases[19] are flagship initiatives of the strategy. Although the revision of the general pharmaceutical legislation is a key element in addressing the objectives of the strategy, its effect needs to be seen with the other actions of the strategy, actions under EU4Health[20] and other relevant EU and national policies.

The **research and development stage** for medicines is supported by Horizon Europe[21] – a key funding programme for EU research and innovation – as well as the Innovative Health Initiative[22], co-funded by Horizon Europe, to promote innovation of medicines, including planned, specific partnerships to address unmet medical need[23] and AMR[24]. The Mission on Cancer[25], together with Europe's Beating Cancer Plan[26] will allow to better support development of cancer treatments. The budget for health research under Horizon Europe amounts to €8.2bn[27]; additional health research is funded by national programmes. In 2016, Member States from which data are available collectively budgeted about €11.3bn for health-related R&D; this figure excludes most tax incentives and funding for higher education and publicly-owned corporations[28]. In the EU, private investment in R&D in medicines and biotechnology has doubled from around €20bn in 2000 to more than €40bn in 2018; in the US, starting from a higher level at €40bn it almost doubled to around €75bn in the same period[29].

The European Health Data Space[30]- under the European strategy for data[31] – will provide a common framework across Member States for access to high-quality real world health data. Use of these will allow progress in research and development of medicines and provide new tools for pharmacovigilance. The revision of the general pharmaceutical legislation will better accommodate **digital tools and the use of health data** fitting the ambitions of 'Shaping Europe's Digital Future'[32]

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[18] mission-letter-stella-kyriakides_en.pdf (europa.eu)

[19] Medicines for children & rare diseases – updated rules, available at https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12767-Medicines-for-children-rare-diseases-updated-rules_en.

[20] E.g. a joint action to support the cooperation between competent authorities by organising trainings, improving scientific assessment capacities and inspections, and an action to contribute to implement the Pharmaceutical Strategy as it concerns supporting Member States in national pricing and reimbursement policies.

[21] Regulation (EU) 2021/695 of the European Parliament and of the Council of 28 April 2021 establishing Horizon Europe – the Framework Programme for Research and Innovation, laying down its rules for participation and dissemination, and repealing Regulations (EU) No 1290/2013 and (EU) No 1291/2013, OJ L 170, 12.5.2021, p. 1.

[22] Council Regulation (EU) 2021/2085 of 19 November 2021 establishing the Joint Undertakings under Horizon Europe and repealing Regulations (EC) No 219/2007, (EU) No 557/2014, (EU) No 558/2014, (EU) No 559/2014, (EU) No 560/2014, (EU) No 561/2014 and (EU) No 642/2014, OJ L427, 30.11.2021, p. 17.

[23] European Partnership on Rare Diseases will develop a European Clinical Research Network to accelerate clinical trials for rare diseases; support access to data, information resources to translate research results into safe and effective medicines; support the scientific work of the International Rare Disease Research Consortium; and integrate basic, pre-clinical and clinical research. This partnership is planned for the work programme 2023/4.

[24] European Partnership: One Health Anti-Microbial Resistance will contribute to achieving the objectives of the European One Health Action Plan against AMR[24] and the World Health Organization Global Action Plan on AMR[24], by reducing the threat of AMR and contribute to achieving the objectives of the Health Emergency Preparedness and Response Authority (HERA). This partnership is planned for the work programme 2023/4.

[25] EU Mission: Cancer, available at EU Mission: Cancer | European Commission (europa.eu)

[26] COM/2021/44 final.

[27] European Commission, Directorate-General for Research and Innovation, *Horizon Europe, budget: Horizon Europe - the most ambitious EU research & innovation programme ever*, 2021, https://data.europa.eu/doi/10.2777/202859.

[28] OECD, Pharmaceutical Innovation and Access to Medicines, OECD Health Policy Studies, 2018.

[29] Analytical report, indicator RI-8, Annex 10.

[30] COM(2022) 197 final.

[31] COM(2020) 66 final.

[32] COM(2020) 67 final.

and the digital transition. By facilitating access to and use of health data the two initiatives together will support the **competitiveness and innovation capacity** of the EU's medical industry.

In 2021, the Health Emergency Preparedness and Response (HERA) was created in the aftermath of the COVID-19 pandemic to prevent, detect and rapidly respond to health emergencies. While HERA can address medicines shortages related to a health emergency, it will not play a role in addressing the challenges of **systemic shortages** targeted by the revision of the general pharmaceutical legislation.

The European One Health Action Plan against **Antimicrobial Resistance** (AMR)[33] aims to reduce AMR and develop alternative treatments or prevent diseases treated with antimicrobials. The revision of the general pharmaceutical legislation would contribute to the implementation of this action plan, together with the planned Council Recommendation on AMR.

The revision will also address **environmental challenges** together with European Green Deal[34] initiatives such as: the EU Action Plan "Towards a Zero Pollution for Air, Water and Soil"[35], the revision of the Urban Waste Water Treatment Directive[36], the revision of the Industrial Emissions Directive[37] and the revision of the list of surface and groundwater pollutants[38] under the Water Framework Directive[39] to include some medicines in order to protect the environment and the public health. Moreover, the EU Strategic Approach to Pharmaceuticals in the Environment[40] lists measures to address challenges from medicine residues.

Finally, this initiative supports the United Nations' **Sustainable Development Goals** (SDGs)[41] and in particular SGD 3 ('ensure healthy lives and promote well-being for all at all ages'), SDG 9 ('build resilient infrastructure, promote inclusive and sustainable industrialisation and foster innovation') and SDG 10 ('reduced inequalities'). The objectives and proposed measures relating to unmet medical need, affordability and unequal access to medicines across the EU are linked to SDG 3 and SDG 10, while those relating to environmental challenges and addressing inefficiencies of the regulatory system contribute to SDG 9.

1.2 Legal context

Directive 2001/83/EC and Regulation (EU) No 726/2004 form one policy intervention, the 'general pharmaceutical legislation' that regulates the authorisation, manufacturing, distribution and monitoring of medicines. It also provides regulatory protection periods to reward innovative medicines.[42] The legislation is based on cooperation and division of responsibilities between the EU and Member States. It provides for common standards but different pathways for an authorisation at EU and at Member State level.[43] Member States are responsible for the authorisation of manufacturers and wholesale distributors and they conduct inspections of companies.

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[33] A European One Health Action Plan against Antimicrobial Resistance (AMR) (June 2017).
[34] COM (2019) 640 final.
[35] COM/2021/400 final
[36] Council Directive 91/271/EEC of 21 May 1991 concerning urban waste-water treatment, OJ L 135, 30.5.1991, p. 40.
[37] Directive 2010/75/EU of the European Parliament and of the Council of 24 November 2010 on industrial emissions (integrated pollution prevention and control, OJ L 334, 17.12.2010, p. 17, and COM(2022) 156 final.
[38] Integrated water management – revised lists of surface and groundwater pollutants (europa.eu).
[39] Directive 2000/60/ EC of the European Parliament and of the Council of 23 October 2000 establishing a framework for Community action in the field of water policy, OJ L 327, 22.12.2000
[40] COM(2019) 128 final.
[41] Home - United Nations Sustainable Development
[42] These regulatory protection periods are described in section 6.1 and in the evaluation SWD, section 3.3, Annex 5.
[43] For certain categories of medicines it is a requirement and for others it is an option for companies to apply for a marketing authorisation granted by the European Commission through the centralised procedure. This authorisation is valid in all Member States and based on a scientific assessment performed by the EMA. Medicines may also be authorised through national procedures. The different authorisation procedures are outlined in Annex 7.

Pharmacovigilance is a shared responsibility. The legislation does not affect the Member States' powers regarding the setting of medicine prices or the inclusion of medicines in the scope of national health insurance schemes.

The general pharmaceutical legislation has touchpoints with other legislation. The ongoing revision of the legislation on medicines for rare diseases and medicines for children is coherent with this revision in it aims to address unmet medical needs and improve patient access to medicines; a description of how the initiatives complement each other can be found in Annex 6.

The Clinical Trials Regulation[44], applicable since 2022, allows a more efficient approval of clinical trials in the EU, while the extended EMA mandate, as part of the European Health Union, strengthens the role of the Agency for a coordinated EU-level response to health crises[45] to ensure access to medicines in such crisis. The EMA fees legislation[46] is currently under revision. The fees support EMA and national competent authorities and contribute to the sustainability of the EU regulatory system.

The revision of the EU legislation on blood, tissues and cells (BTC)[47] is relevant as some substances of human origin are starting materials for medicines. Coherence between the two revisions is key to ensure clarity as to which legislation applies to some BTC based therapies.

For **access to medicines**, in addition to the general pharmaceutical legislation, the intellectual property frameworks (patents and SPCs) as well as the HTA Regulation and the 'Transparency' Directive[48] play a role. The Intellectual Property Action Plan[49] under the Industrial Strategy[50] includes the modernisation of the system of supplementary protection certificates (SPC) in the form of a "Unitary SPC" which does not intend to modify the maximum period of a SPC, but may lead to wider coverage of the SPCs; an impact assessment on these changes is under development.[51] SPCs extend patent rights to protect **innovation** and compensate for lengthy clinical trials and marketing authorisation procedures. At the same time, they impact the effect of regulatory protection periods provided by the pharmaceutical legislation and therefore the entry of generic and biosimilar medicines and eventually **patient access to medicines and affordability**. Member States' decisions on pricing and reimbursement of medicines also influence access. The 'Transparency' Directive regulates procedural aspects of the Member States' pricing and reimbursement decisions but do not

[44] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, OJ L 158, 27.5.2014, p. 1.
[45] Regulation (EU) 2022/123 of the European Parliament and of the Council of 25 January 2022 on a reinforced role for the European Medicines Agency in crisis preparedness and management for medicinal products and medical devices, OJ L 20, 31.1.2022, p. 1.
[46] Council Regulation (EC) No 297/95 of 10 February 1995 on fees payable to the European Agency for the Evaluation of Medicinal Products, OJ L 35, 15.2.1995, p. 1, and Regulation (EU) No 658/2014 of the European Parliament and of the Council on fees payable to the European Medicines Agency for the conduct of pharmacovigilance activities in respect of medicinal products for human use, OJ L 189, 27.6.2014, p. 112. These regulations set out fee amounts and allows for remuneration of the national competent authorities for the contributions to services provided by EMA to companies, e.g. assessment of application for marketing authorisation.
[47] Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC, OJ L 33, 8.2.2003, p. 30, and Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, OJ L 102, 7.4.2004, p. 48.
[48] Council Directive 89/105/EEC, of 21 December 1998, relating to the transparency of measures regulating the pricing of medicinal products for human use and their inclusion in the scope of the national health insurance systems, OJ L 40, 11.2.89, p. 8.
[49] COM(2020) 760 final.
[50] COM(2021) 350 final.
[51] Medicinal & plant protection products – singles procedure for the granting of SPCs

impact on the level of price. The Health Technology Assessment (HTA) Regulation[52] will engage national HTA bodies in joint clinical assessment to provide evidence-based information on the comparative effectiveness of medicines to help national decisions on pricing and reimbursement. This contributes to improve affordability and access across the EU. Annex 14 further describes the multiplicity of factors having an impact and framing access to affordable medicines.

A description of the pharmaceutical ecosystem and legislative landscape can be found in Annex 9 together with a visual overview of the lifecycle of a medicine in Annex 8.

2 PROBLEM DEFINITION

2.1 What are the problems?

The evaluation of the general pharmaceutical legislation showed that the legislation continues to be relevant for the dual overarching objectives of protection of public health and harmonisation of the internal market for medicines in the EU. The legislation delivered on the objectives of the 2004 revision; albeit not to the same extent for all. The objective to ensure quality, safety and efficacy of medicines was achieved to the largest extent, while patient access to medicines in all Member States was achieved only to a limited extent. As to ensuring the competitive functioning of the internal market and attractiveness in a global context, the legislation has performed to a moderate extent. The evaluation found that the achievements or shortcomings of the 2004 revision vis-a-vis its objectives depend on many external factors outside the remit of the legislation, e.g. R&D activities and international location of R&D clusters, national pricing and reimbursement decisions, business decisions and market size. The pharmaceutical sector and development of medicines are global; research and clinical trials conducted on one continent will support development and authorisation in other continents; likewise the supply chains and manufacturing of medicines are global. International cooperation to harmonise requirements to support authorisation exists, e.g. the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. The evaluation identified six shortcomings which are not adequately addressed by the pharmaceutical legislation recognising that they also depend on factors outside its remit:

Medical needs of patients are not sufficiently met

The evaluation showed that the legislation has been less relevant to ensure development of medicines addressing unmet medical needs, including novel antimicrobials. This related to e.g. lack of adequate incentives for innovation by SMEs, academic/industry collaborations. Unmet medical needs with regard to medicines for rare diseases and for children are covered by the parallel revision of the specialised legislations supported by its own impact assessment.[53]

The number of authorised medicines, both innovative and those with well-known active substances (e.g. generic and biosimilar medicines) is constantly on the rise. Since 2005, between 13 and 43 medicines with new active substances have been authorised in the EU every year, and 4-20 of those medicines address unmet medical needs[54]. However, there continue to be diseases with no or only few treatment options, e.g. neurodegenerative or infectious diseases. These unmet medical needs affect millions of EU citizens[55]. In the public consultation[56], all stakeholders found that the

[52] Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU, OJ L 458, 22.12.2021, p. 1.
[53] Cf. Ongoing Impact assessment for Medicines for children and rare diseases: https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12767-Medicines-for-children-rare-diseases-updated-rules_en
[54] Analytical report, indicator RI-9, Annex 10.
[55] The number of people living with dementia in the EU27 is estimated to be 7,853,705 and Alzheimer's disease is the most common form of dementia, Other dementias | Alzheimer Europe (alzheimer-europe.org).
[56] https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12963-Evaluation-and-revision-of-the-general-pharmaceutical-legislation/public-consultation_en.

legislation moderately promotes the development of medicines for unmet medical needs, with industry having the most positive view in that regard. While the general pharmaceutical legislation is not alone responsible for the problem of unmet medical needs[57], it can be instrumental in addressing some of the problem drivers within its remit.

AMR - a specific case of unmet medical need

An important area of unmet medical need is drug-resistant infections due to the emergence and spread of pathogens that have acquired new resistance mechanisms leading to AMR. AMR is responsible for an estimated 33 000 deaths per year in the EU and amounts to an estimated €1.5bn every year in healthcare costs and productivity losses[58]. At the same time the pipeline for novel antimicrobials that can fight resistant pathogens is very weak.[59] There is an apparent market failure and the lack of market incentives has led to underinvestment by big pharma companies in new compounds. Annex 15 further describes the market failure in this area.

Unequal access to medicines across the EU

The evaluation showed that the legislation has limited effect and relevance to ensure patient access to medicines. Access also depends on external factors[60] such as strategic decisions by companies whether and when to launch a product in a given Member State and national pricing and reimbursement policies. However, the general pharmaceutical legislation can have an impact on access through its incentives.

The number of authorised medicines in the EU has increased over time: 1 160 centrally authorised medicines (CAPs) were authorised in the period 2005-2020 and more than 17 000 medicines, primarily generic medicines, were authorised through mutual recognition and decentralised procedures in the same period[61]. However, patient access to medicines varies considerably across the EU[62]. The number of EU countries in which CAPs are launched has been steadily decreasing[63]. Substantial differences have been reported in terms of time to entry on the market[64].

Most medicines are – after authorisation – subject to national pricing and reimbursement decisions and, in particular for innovative and costly medicines, also HTA. The evidence requirements for these decisions (on relative/cost effectiveness of new medicines compared to existing treatments) are different than for the authorisation of those medicines, which is based on a positive benefit-risk balance for patients. Evidence required for HTA or pricing and reimbursement decisions are (often) not generated by companies by the time of the authorisation of the medicine and this may delay access. However, the recently adopted HTA Regulation intends to improve the situation, though its effects could not yet been taken into account in the evaluation and the consultations.

Evidence[65] shows that, whilst in Germany 133 out of 152 (i.e. 88%) new medicines authorised between 2016 and 2019 at EU level were accessible to patients, small Member States such as the Baltic Member States or Member States with comparatively low prices or with low GDP, like Romania, had fewer than 50 of these available[66]. The time to patient access is also significantly

[57] External factors (e.g. scientific barriers) are mentioned in the problem drivers for unmet medical need, see section 2.2.
[58] A European One Health Action Plan against Antimicrobial Resistance (AMR) (June 2017).
[59] Of 43 antibiotics in development, 15 were in Phase 1 clinical trials, 13 in Phase 2, 13 in Phase 3, and two have had new drug applications submitted. Historically, about 60% of drugs that enter Phase 3 will be approved.
[60] See Annex 14 on the factors influencing access to affordable medicines
[61] Analytical report, indicator ACC-1, Annex 10.
[62] Technopolis Evaluation study report, figure 10, 2022.
[63] Kyle, M.K, (2019). The Single Market in Pharmaceuticals. Review of Industrial Organization, 55(1),111-135. https://doi.org/10.1007/s11151-019-09694-6
[64] Bergmann et al., 2016, Ferrario (2016). Access to innovative oncology medicines in Europe. Annals of Oncology, 27(2), 353-356. https://doi.org/10.1093/ANNONC/MDV547
[65] Data from European Federation of Pharmaceutical Industries and Associations (EFPIA) and IQVIA.
[66] Newton et al. (2021). *EFPIA Patients W.A.I.T. Indicator 2020 Survey*.

longer for most of these latter countries, e.g. approximately two years or more after marketing authorisation in Romania compared to four months in Germany. Similar observations were made across different subsets of medicines. As a result, patients may not have had access to any appropriate treatment for their disease.

Although access depends, as explained above, on a multiplicity of factors, most respondents in the targeted survey, except industry agree that there is still room for improvement of the EU legislation in terms of access.

Most of the nationally authorised medicines are generic medicines[67]. Generic and biosimilar medicines can be marketed only after the expiry of regulatory and other intellectual property protection periods of the original medicine. They normally drive prices down and improve access. Low volume markets still experience limited access to generics.

Affordability of medicines is a challenge for health systems

Innovative medicines are often costly. Medicine prices vary significantly between Member States[68]. A study showed that list prices were the highest in Germany and the cheapest in many different EU countries but never in those with lower GDP like Bulgaria or Romania[69]. The medicines analysed were unaffordable for many EU health systems. Pharmaceutical budgets also put pressure on health systems. Medicines in hospitals account for over 20-30% of hospital expenditures and are growing[70].

In 2013-2019, the average household out-of-pocket (including regulated co-payments) share of non-hospital medicines is stable, at around 28-30%, but there are big differences between the MS with countries like Germany and France having shares below 20% and Poland and Bulgaria over respectively 60 and 70%.[71] Out-of-pocket payment for medicines is outside of the remit of the pharmaceutical legislation. Other external factors are described in Annex 14.

Against this backdrop, generic and biosimilar entry can be an important factor in terms of competition, to achieve lower prices, broadening patients' access and alleviating healthcare costs[72]. In the EU, the share of generics in total medicines sales revenue modestly increased (from 13% to 16%) between 2002-2020[73]. An analysis shows that the EU is on a similar trend as other comparable markets (Japan and USA)[74]. Nonetheless, inquiries show that originator companies sometimes use various practices (such as "evergreening" or "killer acquisitions" early in the pipeline) to delay or prevent generic/biosimilar entry. These anti-competitive practices can be prosecuted by EU competition authorities. The evaluation confirms that further efforts can be made to fully exploit the savings generated by the generic and biosimilar competition; although measures in this regard are primarily outside the scope of the general pharmaceutical legislation, the revision can improve the conditions for generic and biosimilar authorisation and competition.

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[67] Study on the experience acquired as a result of the procedures for authorisation and monitoring of medicinal products for human use, EY, January 2020, p. 103.

[68] The desk research suggests for example an almost 11-fold difference between interferone-beta list prices in Germany (€1451.17) and Croatia (€132.77); list prices do not include the confidential rebates (if they exist) or 'price freezes' and may therefore not correspond to the actual price.

[69] Zaprutko T, Kopciuch D, Kus K, et al. Affordability of medicines in the European Union. *PLoS One*. 2017;12(2):e0172753.

[70] European Commission, State of health in the EU: companion report 2019 (ISBN 978-92-76-10194-9)

[71] OECD, Eurostat and World Health Organization (2017), A System of Health Accounts 2011: Revised edition, OECD Publishing, Paris. http://dx.doi.org/10.1787/9789264270985-en).

[72] IMS Health (2015) The Role of Generic Medicines in Sustaining Healthcare Systems: A European Perspective

[73] Evaluation SWD, section 4.1.1.4, Annex 5.

[74] Ibid, footnote 67.

The probability of competition is lower for (a) biosimilars than for generics; (b) products with manufacturing complexity and (c) products with smaller turnover (e.g. for rare diseases).[7576]

According to all stakeholder groups, enabling access to affordable medicines is among the areas where the legislation has been less effective. The rising costs of medicines were key concerns for academics, healthcare professionals, public authorities and civil society stakeholders.

Shortages of medicines

The evaluation showed that medicine shortages are an increasing problem in the EU; a problem that was also experienced during the COVID-19 pandemic. Over the last 10 years, there has been a strong increase in the number of shortages notified in the EU from a few in 2008 to nearly 14 000 in 2019[77]. There are a number of root causes. These include: more complex and diversified global supply chains, quality and manufacturing challenges and commercial decisions or unexpected increase in demand. Evidence shows that medicine shortages are placing a significant burden on health systems, health professionals and are ultimately putting patients at risk of sub-optimal care and health systems at risk of higher healthcare costs[78].

Medicine shortages have also a global dimension due to the global supply chain, where external actions or events impact the supply of medicines in the EU, e.g. the Indian export restriction of certain active substances during the COVID-19 pandemic. Likewise, problems at a manufacturing site may cause shortages in several Member States or the whole EU, depending on the supply chain.

The public consultation confirms the importance all stakeholders (in particular civil society organisations and healthcare professionals) place on medicine shortages. In the targeted survey, civil society, public authorities and health service stakeholders considered that the legislation is the least effective in addressing issues related to security of supply and medicine shortages.

The general pharmaceutical legislation can provide harmonised tools to allow Member States to better handle medicine shortages and thus act as enabler for addressing the problem.

The regulatory system does not sufficiently cater for innovation/unnecessary administrative burden

While the system for authorisation and monitoring of medicines in the EU overall meets the objectives of the general pharmaceutical legislation, rapid scientific and technological developments have resulted in new challenges for the system, which has become more complex over time, as reflected by the expansion of the number of EMA scientific committees and their interactions[79]. New types of medicines (e.g. personalised medicines), approaches and processes, may raise questions about whether they fully fit within the scope of the legislation and can find themselves subject to unintended barriers to innovation, development, production or marketing authorisation. Products combining medicines with technologies regulated under other frameworks (e.g. medical devices, artificial intelligence) or products using new platform technologies[80] face uncertainty about the applicable framework. Likewise, the current framework is not adapted to novel production technologies or methods (e.g. decentralised manufacturing). Borderline issues for ATMPs with the BTC framework, which provides starting materials, were also highlighted in the evaluation.

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[75] SWD(2020) 163 final, p. 58.
[76] Understanding Net Pharmaceutical Expenditure Dynamics in Europe, April 2022, IQVIA.
[77] Analytical report, indicator SM-1, Annex 10. Data only collected for period 2008-2020, during which many Member States put in place new systems or requirements for notification of shortages.
[78] European Commission, Directorate-General for Health and Food Safety, Jongh, T., Becker, D., Boulestreau, M., et al., Future-proofing pharmaceutical legislation: study on medicine shortages: final report (revised), 2021, https://data.europa.eu/doi/10.2875/211485.
[79] COM(2021) 497 final.
[80] When a certain process/method is used to manufacture specific individualised treatments, i.e. adjustments to the medicine are made based on the characteristics of the patient or the causing pathogen.

The consultations showed a consensus between academia/research organisations, patient/consumer organisations, healthcare professionals and industry that the legislation was not flexible enough to accommodate scientific advances, such as real-world data in healthcare. Public authorities noted that medicines regulators need more resources to keep up with the speed of scientific and technological developments and to assess complex therapies appropriately.

Digital transformation has been changing the health sector. However, there is an overall lack of transparency and interoperability; digital expertise and infrastructure are not sufficiently available across the Member States and the EU regulatory network. All stakeholders agreed that EU telematics systems play an important role in contributing to the efficiency of the system, but also identified room for improvement (like a very complex governance system for EU telematics).

An assessment of the current authorisation system[81] identified the need for rationalisation and simplification which the consultations echoed. Stakeholders noted the need for strengthened coordination between bodies responsible for marketing authorisation procedures, clinical trial authorisations, HTA and pricing and reimbursement. Several industry respondents stated that regulatory burden can be costly, duplicative and thus hinder innovation, in particular for innovative SMEs who may struggle with high fee costs, though fees incentives exist for SMEs[82].

Medicines in the environment

While the positive effect of medicine for treatment of diseases is undisputed, pollution caused by medicines is a well-documented risk to the environment and human health, particularly in relation to antimicrobial resistance. Residues of medicines may enter the environment during their manufacturing, use by patients and disposal, with the largest source being the use[83]. Residues of medicines have been found in surface and ground waters, soils and animal tissues across the EU at concentrations depending on the medicine and the proximity of sources[84]. Traces have also been found in drinking water. Residues of medicines in the environment is a global problem[85]. The evaluation confirmed that the current requirement for an environmental risk assessment (ERA) before marketing authorisation has some weaknesses as regards compliance, content and scope.

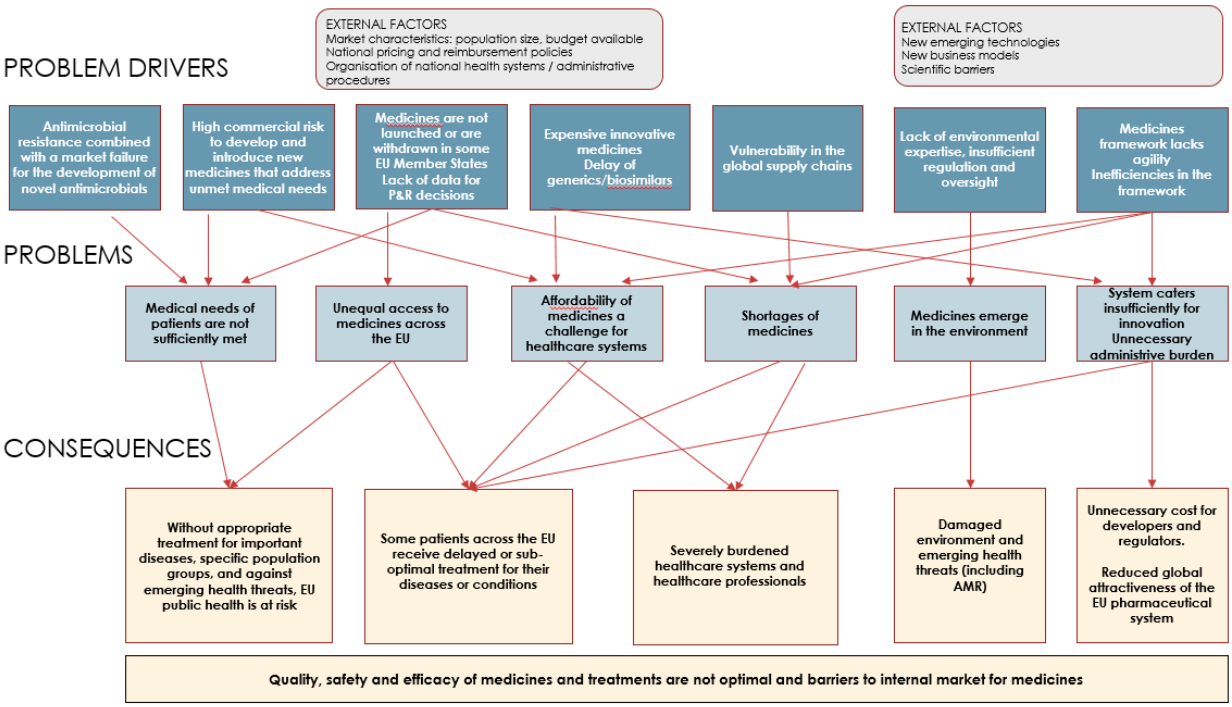
In the targeted consultations, the stakeholders (industry, civil society and public authorities) ranked reducing the environmental impact of medicines among the objectives where the general pharmaceutical legislation had been the least effective. In the public consultation, the stakeholders across the board found that the legislation has performed moderately in ensuring that medicines are manufactured, used and disposed of in an environmentally friendly manner, with citizens, healthcare professionals and public authorities being the most critical.

2.2 What are the problem drivers?

Figure 1 provides an overview of the problem drivers and their link with the problems identified.

[81] COM(2021) 497 final.
[82] Commission Regulation (EC) No 2049/2005 provides for specific support for SMEs, including an SME Office in the EMA and fee reductions and deferrals. Further fee incentives for SMEs are provided in the Rules for implementation of the two fee regulations (Council Regulation (EC) No 297/95 and Regulation (EU) No 658/2014).
[83] COM(2019) 128 final.
[84] Analytical report, indicator E-1, Annex 10.
[85] Idem.

Figure 1 Problem tree diagram for the revision of the general pharmaceutical legislation



The problem drivers that are causing underperformance on the ground are a series of complex, interlinked factors.

Drivers for unmet medical needs

Despite the fast-paced advances in science and technology, scientific barriers prevent the development of medicines to treat or cure some diseases such as Alzheimer's. For unmet needs, there are a series of different drivers, e.g. market failure, complexity of disease pathologies, knowledge gaps in molecular and physiological underpinnings of diseases, high risk R&D. While the EU has a world-leading, research-intensive pharmaceutical industry[86], evidence suggests that R&D costs per new medicine have increased over time with estimates ranging from US$944m to US$2,826m with great variability across therapeutic fields[87]. This is one among the drivers that have increased the commercial risk of developing new medicines for **unmet medical need**.

Big pharma companies tend to disinvest from riskier upstream research and to choose R&D investments that will maximise their future profits through licensing or acquisitions of products that are already in later clinical trial stages with good probability for marketing authorisation, sales and high price.[88] Such business strategies are not always aligned with the public goal of directing efforts towards the greatest unmet medical needs. Furthermore, the pharmaceutical legislation makes no distinction in regulatory incentives granted to highly innovative medicines addressing unmet medical need and those for incremental innovation, such as 'me-too' medicines (similar to existing medicines) without added therapeutic value. This gives less incentive to invest in higher risk development of the former. There is a concentration of investment in areas where there is less

[86] The Pharmaceutical Industry in Figures, Key Data 2021 (EFPIA, 2021).
[87] Simoens, S., & Huys, I. (2021). R&D costs of new medicines: a landscape analysis. *Frontiers in medicine*, *8*, available at https://www.frontiersin.org/articles/10.3389/fmed.2021.760762/full.
[88] EPRS_STU(2021)697197_EN.pdf (europa.eu): European pharmaceutical research and development. Could public infrastructure overcome market failures?

financial risk, e.g. oncology. When companies invest in less risky areas, even incremental innovation can lead to an economically viable or profitable product.

The **growing resistance of pathogens to antimicrobials (AMR)** combined with the weak global pipeline of major new classes of antimicrobials are a special driver for unmet medical need. A growing market failure derives from the fact that the typical cost of surpassing the scientific challenges involved in developing new antimicrobials is very high and at the same time the typical income and profit that can be derived from sales of these products are very limited because healthcare systems want to keep new antimicrobials in reserve or limit their use so as not to fuel the vicious cycle of AMR, by inappropriate use of already authorised antimicrobials.

Drivers for access to medicines

A key **access problem driver** is that authorised **medicines are not launched in all Member States or are subsequently withdrawn**. Currently, companies have the choice where and when to launch centrally authorised medicines, the legislation only requires them to place their product on the market in at least one Member State within three years of its authorisation (the so-called 'sunset clause'). Other than that, companies have a free hand; this creates an unpredictable situation for patients and Member States. With some Member States companies enter into pricing and reimbursement negotiations only very long time after marketing authorisation or not at all. The decision for the company to launch and when depends on different factors for example the size of the patient population, or national pricing and reimbursement policies, and the organisation of health systems. These factors influence whether the company can successfully pass a HTA in that Member State and finally negotiate a price and a reimbursement status for the product.

Access may also differ due to organisational differences in Member States (different medical protocols, access to specific equipment/infrastructure needed for administration, different characteristics of the health systems).

The pharmaceutical legislation has no direct influence on HTA and pricing and reimbursement processes or the organisation of the national health systems. However, the general pharmaceutical legislation and its system of regulatory incentives can be an enabling factor to improved access by incentivising market launch by companies, strengthening the position of national pricing and reimbursement bodies, facilitating collaboration among decision makers along the lifecycle of a medicine and by increasing competition from generics and biosimilars.

For a more detailed analysis on the factors and dynamics behind the market launch, the access chain, HTA, pricing/reimbursement process and on pharmaceutical expenditure please refer to Annex 14.

Withdrawals of medicines disrupt the established access chain (from authorisation to entry into the health system). An available product abruptly or gradually withdrawn from the market (often for commercial reasons) can create **shortages** and leave patients without treatments.

Drivers for affordability of medicines

Pharmaceutical expenditure is largely subsidised by national health systems in order to ensure the adequate provision of medicines to all their respective citizens. New, highly **innovative medicines** may place pressure on public budgets due to their prices. Therefore, Member States adopt measures to regulate the prices of medicines and the conditions of their public funding based on their exclusive competence in this field (Article 168 TFEU). Member States follow different **price and reimbursement policies** and the pharmaceutical markets remain very fragmented by country (for a review of pricing policies[89]). The External Reference Pricing (ERP) policy, for which the price set for the same product in one or several countries is used as a benchmark for setting the product's price in a given country, is the most frequently used pricing policy in Europe. As a consequence of

[89] WHO guideline on country pharmaceutical pricing policies, Geneva: World Health Organization; 2020.

differences in prices, the use of ERP and parallel import, and differences in market size, the availability and entry date of medicines strongly differ among Member States.

The prices by country do not depend only on the government regulation (such as price controls and reimbursement decisions) but also on several other factors, such as income per capita, the size of the market, the characteristics of the product (innovative or old, its therapeutic advantages etc.), the patent status, the presence of competitors and research costs incurred (also for unsuccessful development of medicine)[90]. However, there is a lack of transparency on R&D costs or public contributions to these costs. While R&D costs are not relevant for the assessment of a medicine's benefit-risk balance, information on such costs are relevant for the downstream actors and may facilitate their decision-making.

Delay in generic and biosimilar entry is also a driver for expensive innovative medicines.

The general pharmaceutical legislation has only an indirect impact on the affordability of medicines by facilitating competition and early market entry by generic and biosimilar medicines. In a similar way, it streamlines procedures and makes the regulatory framework more efficient thereby lowering costs for authorisation or manufacturing which could have an impact on the price of the medicine.

Drivers for shortages of medicines

Vulnerability in the global supply chains has arisen from global industry consolidation with increased complexity in supply chains, in which many different intermediate suppliers may be connected, and, in particular for generic medicines, from reliance on a few, specialised overseas suppliers that produce at lower prices. In addition, the notification and obligation to ensure appropriate and continued supply, varies across Member States with e.g. 4 months in advance notification of shortages in Italy and at least 6 months in Romania[91].

While Member States have already introduced a variety of actions at the national level to help protect their security of supply, the impact of these measures on preventing and mitigating the impact of shortages is not yet sufficiently understood.

Drivers for medicines into the environment

The **lack of relevant or insufficient regulation and oversight** currently influences the effects medicines use may cause for the environment, while a lack of environmental expertise influences the understanding of the effects on the environment from medicines. The largest source of medicines entering the environment is the use of medicines; due to the chemical and/or metabolic stability of some medicines, as much as 90% of the active substance is excreted or washed off into the environment in its original form[92]. Pharmaceuticals mainly reach the environment through:

- the discharge of effluent from urban waste water (sewage) treatment plants – containing excreted pharmaceuticals as well as unused pharmaceuticals thrown away into sinks and toilets, despite the existence of collection schemes;
- the spreading of animal manure; and
- aquaculture, in which pharmaceuticals are often dispensed with the animal feed.[93]

Another source is the discharge of effluent from manufacturing plants (especially those outside the Union) with potential impacts that may significantly effect on a local scale when manufacturing

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[90] Zaprutko T, Kopciuch D, Kus K, et al. Affordability of medicines in the European Union. *PLoS One*. 2017;12(2):e0172753.
[91] European Commission, Directorate-General for Health and Food Safety, *Future-proofing pharmaceutical legislation: study on medicine shortages: final report (revised)*, 2021, https://data.europa.eu/doi/10.2875/211485.
[92] COM(2019) 128 final.
[93] Idem as 92.

emissions of wastewater are inadequately managed.[94] Environmental legislation, such as the Urban Waste Water Directive – currently under revision – and other environmental legislation and initiatives mentioned in section 1.1, is the main instrument for addressing reduction of medicines residues and hence the environmental impact of the industry; however, not even the best and most expensive current wastewater treatments are 100% effective. The measures in this revision complement environmental legislation.

Drivers for lack of innovation and inflexible regulatory framework

The rapid pace of the scientific and technological development is a driver for – and an external factor to – the problem that the regulatory system does **not sufficiently cater for innovation**. The general pharmaceutical legislation is often prescriptive, and it takes a long time to amend it. Hence, the **medicines framework lacks agility** to respond to rapid developments.

Inefficiencies in the regulatory framework were identified in the evaluation, e.g. redundant requirements like the 5-year renewal of marketing authorisation, leading to unnecessary administrative burden. In addition, there is duplication of assessment by the medicines authorities, for instance when different companies apply for authorisation of the same product with the same clinical trial in different procedures. There is insufficient pan-European digital infrastructure and legal basis for optimal use of electronic tools for companies or medicine authorities which contributes to a loss of competitiveness. Better use of digitalisation in the framework, e.g. through electronic product information, could help combat shortages, increase access in smaller markets and also support competition, while improving information on medicines.

2.3 How likely is the problem to persist?

If no EU action is taken, the problems described will persist. While more medicines are expected to be authorised (for CAPs this might increase to 40-60 medicines containing new active substances per year[95]), these medicines will not necessarily address unmet medical needs to a greater extent than today. For example, recently approved antibiotics[96] and the clinical pipeline are insufficient to tackle the increasing emergence and spread of antimicrobial resistance[97]. The market failures in this area will not be corrected without interventions on several fronts, including the general pharmaceutical legislation. The persistence of the problems is also confirmed by some of the megatrends identified by the EU Joint Research Centre[98]. The megatrend on shifting health challenges describes demographic changes and environmental challenges that could create new unmet medical needs and public health burdens as demonstrated by the COVID-19 pandemic.

Authorised medicines will continue to be inaccessible at affordable prices in some Member States. The 'access chain' mechanism mentioned above and analysed in Annex 14 is affected by deficiencies that are systemic in nature and some of the 'links' lie outside the remit of this legislation. Nevertheless, the analysis of the policy options in section 6 shows that the revision of the legislation can act as a key enabler for access and can influence affordability. The policy interventions in the legislation shall be complemented by other actions of the pharmaceutical strategy, e.g. best practice exchange between Member States on pricing, payment and procurement.

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[94] Larsson DGJ. 2014 Pollution from drug manufacturing: review and perspectives. *Phil. Trans. R. Soc* ***369****:20130571*.
[95] Described in section 5.1.1.
[96] Since 2015. 11 antibacterials with new active substance have been granted a Union marketing authorisation, though none of these products constituted a new class of antibiotic.
[97] Antimicrobial products in clinical development for priority pathogens (April, 2021), 68 products are in development (41 antibiotics and 27 non-traditional antibacterial agents) see https://www.who.int/observatories/global-observatory-on-health-research-and-development/monitoring/antibacterial-products-in-clinical-development-for-priority-pathogens.
[98] The Megatrends Hub | Knowledge for policy (europa.eu)

Since new scientific and technological developments will continue, some problems may exacerbate if the legislation is not future-proof. Current work-arounds which are based on 'creative' interpretation will become bottlenecks, especially for complex products. Borderlines between product categories may be more blurred and determination of applicable legal frameworks and their interaction may become complex, leading to longer development or authorisation processes for innovative medicines and thus a longer time to reach patients. This impacts negatively innovation while some innovative products may remain unregulated with negative effect on public health.

If the efficiency of the regulatory system will not be improved and administrative burden not reduced, e.g. by digitisation, valuable resources might not be available to facilitate the development and the assessment of innovative medicines. Likewise, resources might not be available to invest in the expertise needed to cope with new scientific and technological developments. For the industry, there might be less investment in new medicines and hence fewer new medicines authorised, reduced innovative capacity and competitiveness. The megatrend on accelerating technological change and hyperconnectivity is particularly relevant both in terms of development and innovation of medicines and of digitisation of the regulatory system.

Likewise, the problem of medicine residues in the environment will persist if no EU action is taken with risks to flora, fauna and habitat due to the pharmacological characteristics of the active substances. The megatrend on increasing demographic imbalances with the ageing population in the EU may exacerbate the environmental challenges from medicines as elderly people tend to use more medicines than young people; this could also put further pressure on national health systems.

3 WHY SHOULD THE EU ACT?

3.1 Legal basis

The general pharmaceutical legislation is based on Articles 114 and 168 of the Treaty on the Functioning of the European Union (TFEU). These articles provide the legal basis for the EU to adopt measures which have as their object the establishment and functioning of the internal market (Article 114(1)) as well as setting high standards of quality and safety of medicinal products (Article 168(4)(c)). While the internal market and common safety concerns in public health matters fall within a shared competence of the EU and Member States, once the EU adopts harmonised legislation in such an area, Member States can no longer exercise their own competence. This is the case for the general pharmaceutical legislation. Any future legislative proposals, supported by this impact assessment, will be based on Articles 114(1) and 168(4)(c) TFEU. It will also consider Article 35 of the EU Charter of Fundamental Rights that provides that the Union is to ensure a high level of human health protection in the definition and implementation of Union policies.

As per Article 168(7) of the TFEU, Member States are responsible for the definition of their health policy and for the organisation and delivery of health services. Consequently, coverage and pricing decisions for medicines are outside the scope of the legislation.

3.2 Subsidiarity: Necessity of EU action

Diseases do not know borders. Common provisions for the authorisation of medicines constitute a cross-border issue for public health that affects all Member States and thus can effectively be regulated only at EU level, given that the authorisation of medicines is fully harmonised at EU level.

The objectives this revision intends to achieve benefit all Member States. EU action relies also on the single market to achieve a stronger impact as regards access to safe, effective and affordable medicines, as well as the security of supply across the EU. National actions are likely to create disharmonised solutions resulting in fragmentation, and possibly exacerbate some of the problems to be solved, distort competition and increase administrative burden for the pharmaceutical companies, which often operate in more than one Member State. An example of fragmentation is the additional

and non-harmonised measures introduced by Member States to prevent and mitigate medicines shortages[99]. A harmonised approach at EU level also provides greater potential for incentives to support innovation and for concerted action for development of medicines in areas of unmet needs.

The legislation respects Member States' exclusive competence in the provision of health services, including pricing and reimbursement policies and decisions. In this respect, the Pharmaceutical Strategy provides for supporting non-legislative actions such as cooperation mechanisms, e.g. through a group of competent authorities, based on mutual learning and best practice exchange on pricing, payment and procurement policies. These exchanges can be facilitated at EU level.

3.3 Subsidiarity: Added value of EU action

This initiative revises a system with recognised EU added value for the EU patients/citizens, pharmaceutical industry and medicines authorities through e.g. timely authorisation, patient access and continuous supply of innovative and established medicines and strong cooperation[100].

This revision is expected to bring further benefits by addressing unmet medical needs and contributing to reducing the unequal patient access to medicines across the EU. At the same time, simplification and streamlining of processes are expected to reduce administrative burden for companies and authorities and hence improve efficiency and attractiveness of the EU system.

This revision can influence positively the competitive functioning of the market through the review of the incentives and other measures to facilitate early entry on the market of generic and biosimilar medicines and hence improve patient access and affordability.

These benefits and cost-savings can best be achieved by EU action, while recognising that external factors such as national pricing and reimbursement policies and company decisions to launch medicines have great impact on patients' access to medicines. Furthermore, science and technological developments, as well as R&D policies and company investment decisions influence innovation, especially for unmet medical needs.

The measures to support security of supply under this initiative relate to the responsibilities of marketing authorisation holders and supply chain actors like wholesalers. Those actors are already covered by the EU pharmaceutical legislation. However, measures supporting security of supply go beyond legislative measures; many actions do actually take place already at national level and will continue to do so. National and EU levels are not alternatives to each other, but complementary.

In a few instances, the evaluation identified problems with a harmonised implementation of the Directive across Member States[101]. However, these problems relate to vague legal wording of the respective provision rather than the legal instrument used. Moreover, in 2019, a REFIT Platform Opinion[102] considered a suggestion to turn the Directive into a Regulation, though that suggestion did not receive overall support. The opinion showed that many Member States considered the system sufficiently harmonised and would not see a need for a Regulation.

4 OBJECTIVES: WHAT IS TO BE ACHIEVED?

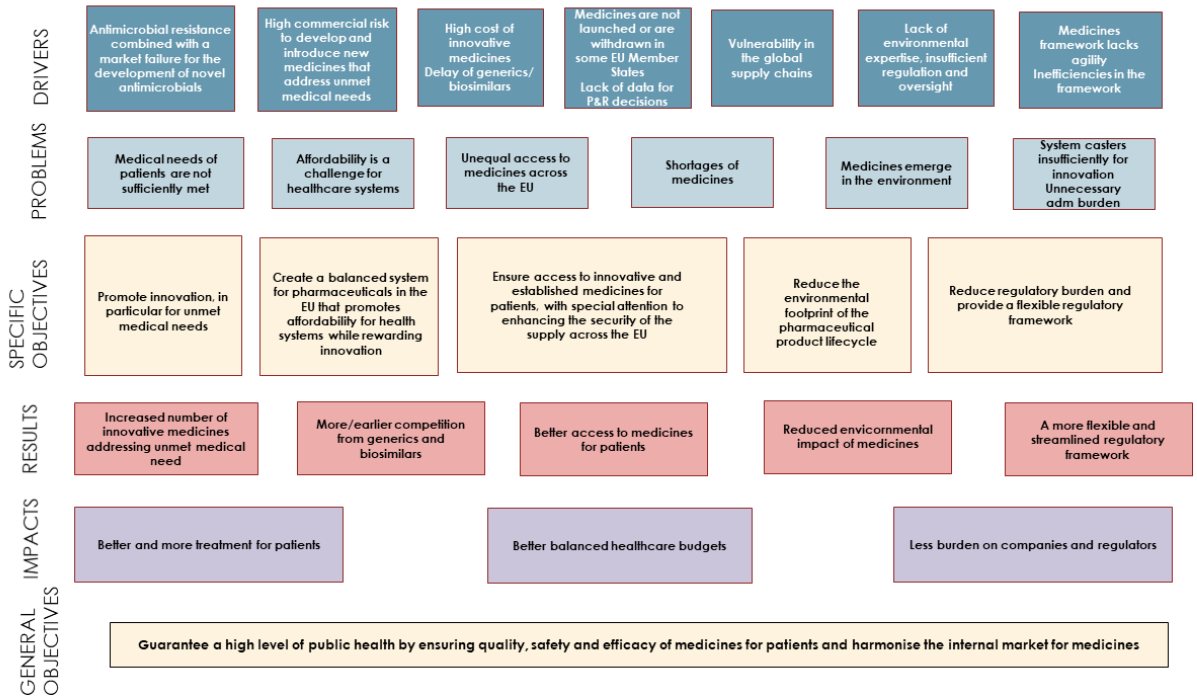
4.1 Introduction

This section sets out the general and specific objectives as well as the logic (Figure 2) underpinning the revision. It addresses the problems identified, and provides a focus for assessing and comparing

[99] European Commission, Directorate-General for Health and Food Safety, Future-proofing pharmaceutical legislation : study on medicine shortages : final report (revised), 2021, https://data.europa.eu/doi/10.2875/211485
[100] Evaluation SWD, section 4.2, see Annex 5.
[101] E.g. application of the Bolar provision – see page 7 of the evaluation SWD
[102] https://wayback.archive-it.org/12090/20200308120955/https:/ec.europa.eu/info/sites/info/files/xi.9.a_medicinal_products_for_human_use.pdf

the likely cost-effectiveness of the selected policy options. The two legislations constituting the general legislation make up a single intervention logic in this policy area.

Figure 2 Intervention logic for the general and specific objectives, problem drivers and problems



4.2 General objectives

The general objectives of the revision remain unchanged in that the general pharmaceutical legislation aims to 'guarantee a high level of public health by ensuring the quality, safety and efficacy of medicines for EU patients' and harmonise the internal market.

4.3 Specific objectives

In response to the problems identified, this revision aims to:

1. **Promote innovation, in particular for unmet medical needs**

The objective is to promote innovation with special focus on medical conditions not yet addressed and which represent a significant EU health burden (unmet medical needs). The revision should enable major biomedical research advances and ensure a pipeline of innovative new medicines for use across the EU. It should also support pharmaceutical R&D and strengthen the competitiveness of the research-based EU pharmaceutical sector.

The objective is also to address the market failure related to the development of novel antimicrobials through novel incentives that can finance the research required while respecting the need for a as limited as possible use of antimicrobials to reduce the tendency of pathogens to develop resistance.

2. **Create a balanced system for pharmaceuticals in the EU that promotes affordability for health systems while rewarding innovation**

This objective aims to enable competition, to promote affordability of medicines for health systems across the EU and ensure healthcare costs are sustainable for Member States. Affordability should not though be promoted at the expense of innovation, which also benefits patients. Thus, the underlying ambition is to create a balance where, on the one hand, innovation is rewarded, and on the other hand, faster market entry of generic and biosimilar medicines is facilitated, as a means to

improve competition across the EU. This is expected to drive down costs for medicines with the additional benefit of strengthening the EU generic and biosimilar industry.

Affordability is a new objective of the revision, which can only indirectly be impacted by the general pharmaceutical legislation.

3. Ensure access to innovative and established medicines for patients, with special attention to enhancing security of the supply across the EU

This objective aims to promote equal access to medicines for all EU citizens, including in smaller Member States, after a timely authorisation under the EU pharmaceutical system. After a medicine has been developed and become available after a timely authorisation under the EU pharmaceutical system, patient access has two dimensions: (i) equal access to/market entry of innovative medicines across the EU and (ii) continuous supply and limited shortages of all medicines. As regards the first, the aim is to provide a motivation to companies to rapidly reach an agreement with Member States and engage Member States in effective negotiations. Facilitating competition from generic and biosimilars will also serve the same objective. As regards the second dimension (shortages and keeping products on the market), the aim is to enhance and harmonise notification requirements and obligations to ensure appropriate and continued supply across Member States.

4. Reduce the environmental impact of the pharmaceutical product lifecycle

This objective aims to reduce the environmental impact of pharmaceuticals through minimising medicine residues in the environment from their production, use, and disposal. This would entail an enhanced assessment of environmental risks of medicines and appropriate risk mitigation measures, including on their prudent use, especially for AMR.

5. Reduce the regulatory burden and provide a flexible regulatory framework

This objective aims to create a more flexible regulatory framework, to future-proof innovation and reduce regulatory burden. Through simplifying and integrating regulatory requirements and pathways and reducing burden for industry and public authorities alike, this objective aims to increase the attractiveness of the EU regulatory system. The goal is to provide clarity on the appropriate regulatory pathway, reduce approval times and costs while maintaining high standards and robust assessment of the quality, safety, and efficacy of medicines. Leveraging digital technology and the use of electronic product information could support this objective.

Objectives 1, 2 and 5 work in synergy for promoting innovation as do objectives 2, 3 and 5, with a range of measures to achieve access to affordable medicines. Trade-offs have to be considered between objectives 4 and 5 as measures to reduce the medicine residues in the environment are likely to increase the administrative burden. Trade-offs have also to be carefully considered for measures under objective 3 to address the risk of shortages while reducing regulatory burden. Trade-offs between achieving access (objective 3) through possible costs of additional market launches and affordability (objective 2) may also be necessary. Trade-offs are also inherent in objective 2 between rewarding innovative medicines and affordability often achieved by generic/biosimilar competition.

The specific objectives are consistent with the European Green Deal and Digital agenda principles and with the right of access to preventive health care and the right to benefit from medical treatment set out in the EU Charter of fundamental rights[103]. In particular objectives 1 and 3 on innovation including for unmet medical needs and on access to medicines will have a positive effect on the access of patients to the medicines they need which relates to Article 35 of the Charter of fundamental rights of the EU which establishes the right to benefit from medical treatment under the conditions established by national laws and practices and a high level of human health protection in

[103] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A12012P%2FTXT

the definition and implementation of all the Union's policies and activities. Objective 4 which is expected to reduce medicines' residues in the environment from their manufacturing, use and disposal is in line with the objectives set out by Article 37 on environmental protection.

5 WHAT ARE THE AVAILABLE POLICY OPTIONS?

5.1 What is the baseline from which options are assessed?

The baseline is represented by the business-as-usual scenario, that is, the situation where no policy changes are made.

The current system provides 8 years of data protection and 2 years of market protection for all innovative medicines, to give time to developers to recoup their investment by delaying the entry of generic or biosimilar medicines. Other incentives also exist in parallel that delay generic/biosimilar competition (patent, SPC, orphan market exclusivity, paediatric protection extensions), usually offering a longer than 10-year protection if a medicine is eligible. However, the regulatory data and market protection is the broadest in terms of eligibility, as it applies to all innovative medicines, and it is almost impossible to infringe it[104].

The current legislation also provides an additional 1 year regulatory protection for a new indication with significant clinical benefit, allowing thus a maximum of 11-year protection. The revision does not consider changing this incentive. Therefore, this incentive is not presented in the options.

Currently, there are no special incentives or obligations for the development of new antimicrobials or prudent use of existing ones, nor for conducting comparative clinical trials.

There are no incentives or obligations on MAHs to place their products on the markets that do not offer a sufficient business case. In essence, even when receiving an EU-wide marketing authorisation, a company is completely free to choose where and when it will market its product. There is no predictability for Member States who have no way of obliging the company to initiate negotiations for pricing and reimbursement. The steps from a medicine's marketing authorisation to access and the influencing factors are described in Annex 14. There is no requirement for MAHs to be transparent about public contribution to R&D costs either.

With regard to shortages, the current system focuses on notifying supply disruptions; it obliges MAHs to notify competent authorities 2 months in advance if they expect a temporary or permanent withdrawal of a medicine. Moreover, MAHs and wholesalers have to ensure appropriate and continued supplies of medicines, however without effective means to enforce the obligations.

The ERA is the main mechanism within the current legislation for addressing environmental impact of pharmaceuticals. It is required for all new MA applications and covers the environmental risks of the use, storage and disposal of pharmaceuticals. It does not include environmental effects of manufacturing. While it provides data to assess the impact of medicine residues released into the environment, there are gaps in timely enforcement and possible risk minimisation measures.

SMEs have a fundamental role in the development of medicines. According to a recent report from IQVIA[105], emerging biopharma companies (defined differently than SMEs in the EU, but essentially the same category) were responsible for a record 65% of the molecules in the R&D pipeline in 2021, up from less than 50% in 2016 and 33% in 2001. The trend is that small companies dominate the earlier development stages, which are not too expensive but very risky. Once the molecule reaches a

[104] Before authorising a generic/biosimilar product, national competent authorities check against the data protection or market exclusivity of the reference medicine and do only authorise the generic if these protections have expired.
[105] 'Global Trends in R&D: overview through 2021,' IQVIA Institute for Human Data Science, February 2022.

certain maturity and still looks commercially promising, the SME typically partners[106] with big pharma companies, which come in at the stage of the expensive late-stage clinical trials, marketing authorisation and market launch that often require vast capital and global infrastructure.

5.1.1 Projections

The life sciences sectors continue to invest in and advance innovative therapeutics and vaccines, the total number of products that are in active development globally exceeds 6 000, up 68% over the 2016 level.[107] Rich pipelines translate to more medicine authorisations, and we assume that the current annual 30-40 authorisations of medicines with new active substances in the EU will expand to 50-60 in the next 15 years. In our **dynamic baseline**, we will take the middle value at the middle of the next 15-year period, **45 innovative medicines per year** to analyse the impacts of the various policy measures proposed.

Against the backdrop of the overall positive outlook for innovation, research efficiency declines and it costs more money and requires more failures to develop a new medicine[108]. Investments in R&D are driven by commercial interest rather than public health needs, leaving important unmet medical needs unaddressed. We expect that **15-20%** of the new innovative medicines, or **7-9 medicines per year will address a real unmet medical need** without changes to the baseline, based on the current ratio of accelerated assessments at the EMA[109].

According to WHO, drug-resistant bacterial diseases already cause at least 700 000 deaths globally a year, including 230 000 deaths from multidrug-resistant tuberculosis, a figure that could increase to 10 million deaths globally per year by 2050 under the most alarming scenario if no action is taken and no new antibiotics are developed and authorised.

Regarding access to medicines, a IQVIA survey[110] shows no major improvement over the last year, with a **90% variance** between Northern and Western European countries and Southern and Eastern European countries **in terms of patient access to new medicines**, which also largely **corresponds** to the launch patterns according **to market size and purchasing powers** described in section 2.1 and Annex 14 due to pricing and reimbursement policies. The average delay between market authorisation and patient access can vary by as much as a factor of seven across EU, from as little as 4 months to 29 months. Maintaining the baseline would likely conserve the problem at today's level.

Available evidence suggests that across the EU the frequency of shortages and their impact on patients and healthcare providers is increasing[111].

If no changes are made to current requirements, the effect of the ERA to manage environmental risks would remain limited. The main effect to reduce medicines in the environment should come from environmental legislation.

5.2 Description of the policy options

In order to respond to the specific objectives, we considered more than 70 potential policy measures deriving from the consultation process and initial analysis. These measures were organised around nine policy blocks reflecting the objectives of the revision and its broad scope[112].

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[106] Big pharma may acquire the rights for the product, the whole company, or they develop, authorise and market the medicine in a joint partnership (e.g. the Pfizer-BioNTech COVID-19 vaccine).
[107] 'Global Trends in R&D: overview through 2021,' IQVIA Institute for Human Data Science, February 2022.
[108] idem
[109] Annex 5 – Evaluation SWD, p.22
[110] EFPIA Patients WAIT Indicator 2021, see: https://www.efpia.eu/media/636821/efpia-patients-wait-indicator-final.pdf
[111] European Commission, Directorate-General for Health and Food Safety, Future-proofing pharmaceutical legislation : study on medicine shortages : final report (revised), 2021, https://data.europa.eu/doi/10.2875/211485

In a second step, taking into account the preliminary evaluation findings, we designed the three high-level options which represent alternative ways to reach all the objectives of the revision. Each option is constructed around specific underlying principles behind the grouping:

- Option A builds on status quo and achieves the objectives mainly through new incentives;
- Option B reaches the objectives through more obligations and oversight;
- Option C adopts a 'quid pro quo' approach in the sense that positive behaviour is rewarded and obligations are only used when there are no alternatives.

Each option contains pivotal and non-pivotal measures. Non-pivotal measures are complementary to the pivotal ones and form an integral part of the policy options. A thorough multi-criteria impact analysis for each policy measure, based on data, literature review and stakeholder feedback can be found in Annex 11.[113] Finally, the options are complemented by horizontal measures. Contrary to the non-pivotal measures, they apply across the board and deliver on simplification and innovation.

The IA report focuses on the 'pivotal' measures and the 'pivotal horizontal measures'. These pivotal measures were selected on the basis of the magnitude of their impacts and their political importance. **Table 1** shows how the pivotal measures map on to the specific objectives.

[112] Directive 2001/83/EC merged 11 prior directives related to medicinal products, and together with the Regulation (EC) No 726/2004, consists of 220 articles, offering numerous "levers" to adjust the policy.

[113] To give an example, a pivotal measure to support market access is making the last 1 or 2 years of regulatory data protection subject to market launch in all EU countries and this is discussed in the main body of the IA. Access in all Member States will be supported by other measures, such as facilitating multi-country packs to make launches in smaller Member States easier, but those measures are rather considered in Annex 11.

5.2.1 Tabular overview of policy options

Table 1 Mapping of **pivotal elements** to the **specific objectives**

Objective	**Baseline**	**Option A**	**Option B**	**Option C**
Promote innovation, in particular for unmet medical needs.	8 years DP +2 years MP	8 years DP +2 years MP Special incentive: +1 year DP for medicines that address UMN +6 months DP to include comparative trials Digitalization, simplification elements from horizontal measures	6 years DP +2 years MP Special incentive: + 2 years DP for originators that address UMN. Digitalization, simplification elements from horizontal measures	6 years DP +2 years MP Special incentive: +1 year DP for medicines that address UMN + 6 months DP for comparative trials Digitalization, simplification elements from horizontal measures
Incentives to promote the development of novel antimicrobials	No special incentives for the development of antimicrobials	Transferable exclusivity vouchers for antimicrobial products	Pay or play model for antimicrobial products	Transferable exclusivity vouchers for antimicrobial products
Create a balanced system for pharmaceuticals in the EU that promotes affordability for health systems while rewarding innovation	Generic and biosimilar entry after DP/MP periods are over providing a predictable framework for competition from generic and biosimilar medicines.	Baseline + additional rewards for innovation and access. Comparative trials may lead to public cost savings.	Earlier entry of generics and biosimilars with 2 years shorter protection than baseline +2 years MP for medicines with no return on investment. Require public transparency on any relevant public contribution or funding, including of research and development costs	If market launch condition not met, earlier entry of generics and biosimilars Require transparency on public contribution to R&D costs in relation to clinical trials included in the MA application Comparative trials may lead to public cost savings.
Ensure access to innovative and established medicines for patients with special attention to enhancing security of supply across the EU	Currently no obligation or incentive to launch in a particular or group of MS	+6 months additional protection period if centrally authorised product is placed on market in all MSs within 6 years of the MA (milestone incentive); and allow generic competition if not launched in majority of MS within 5 years of MA (disincentive)	Obligation to place a centrally authorised medicine on the market in the majority of MS (small markets included) within 5 years	+2 years (or 1) DP extension if medicine is placed on all EU markets within 2 years of authorisation and appropriately and continuously supplied
	Obligation to notify a withdrawal 2 months before the interruption in market supply of the product	Notification requirement same as in baseline	Notification requirement same as in baseline	Improve data on medicines shortages, through adequate notification periods for withdrawals and serious shortage risks; shortage prevention, increased transparency of the supply chain, mitigation plans for all medicines and stockpiling of critical medicines Monitoring of shortages is reinforced with a mechanism of information exchange between MS.
Reduce environmental impact of the pharmaceutical product lifecycle	An ERA is required for all new MA applications. Potential risks from medicines to the environment are assessed by regulators and precautionary measures are taken	Same as baseline ERA	Strengthen the conditions of use for medicines and ERA requirements, including the assessment of the environmental risk of manufacturing and its impact to AMR	Same as option B with the inclusion of AMR aspects in GMP.
Reduce regulatory burden, and provide a flexible regulatory framework	Not applicable / non legislative measures	Horizontal measures* *The horizontal measures are applicable to all options, for details please refer to section 5.2.5.	Horizontal measures*	Horizontal measures*

Notes: AMR=antimicrobial resistance; DP=data protection; EMA/HMA= European Medicines Agency/Heads of Medicines Agencies; ERA= environmental risk assessment; GMP=good manufacturing practice; MA= marketing application; MP=market protection; MS=member state; R&D=research and development; UMN=unmet medical need

5.2.2 Policy Option A

Option A addresses the identified problems through **incentives** rather than setting further obligations coupled with a stronger enforcement of existing obligations and information requirements.

To stimulate **innovation**, Option A maintains the current system of regulatory incentives (8 years data + 2 years market protection), supplemented by a targeted incentive, an additional 1 year of regulatory data protection for products addressing unmet medical need (UMN). Clarifications of the scope and new definitions should facilitate innovation. It also foresees the introduction of a new **incentive for the conduct of comparative trials**, which bring a more robust evidence base for the assessment of effectiveness of new treatments and facilitate decision-making downstream in the lifecycle of medicines.

Option A stimulates the development of novel **antimicrobials** that can fight resistant pathogens through **transferable exclusivity vouchers**. A transferable regulatory protection voucher (transferable exclusivity voucher) allows the developer of a novel antimicrobial that reduces AMR to benefit from an additional year of RP on another product in their portfolio or sell the voucher to another company. This is a measure supported mostly by industry as a way to underpin the substantial R&D costs of bringing new classes of antimicrobials to the market[114]. This will be supported by measures on harmonisation of the summary of product characteristics for nationally authorised antimicrobials to support good prescription practices.

Option A promotes patient **access** with a 6 month regulatory data protection incentive if a product is placed on the market in all Member States within 5 years of MA. The rationale behind the measure is that MAHs can be encouraged to increase the number of markets in which they launch products or accelerate the timeframe within which they do so, by offering them a reward in exchange.

Measures on **security of supply** retain the current requirement for notifications of withdrawals (at least two months in advance).

The current **ERA requirements** continue with an additional obligation to include the information on the environmental impact of supply chain actors in the application dossier. The latter proposal is part of the package of suggestions to support quality and manufacturing aspects (QMC) for medicines.

Among the **non-pivotal measures** of Option A are a non-binding system for scientific assessment of evidence for repurposing off-patent medicines to include new indications for allow for innovation, measures to facilitate multi-country packs to enhance access and inclusion of new manufacturing methods into the framework to both ensure best quality manufacturing and to cater for innovation.

5.2.3 Policy Option B

Option B uses **more obligations** to address the specific objectives rather than incentives. This option explores stronger monitoring mechanisms and increased obligations with interventions at different milestones in the lifecycle of a medicine to foster patient access, affordability and security of supply.

To stimulate **innovation**, especially for unmet medical needs, it introduces a modulated **system of incentives**, with a reduction in the current standard regulatory protection periods. The new standard protection[115] for all originator medicines would consist of 6-years data protection and 2-year market protection. New originator medicines with a demonstrated ability to address UMN would benefit from an additional 2 years of data protection, thus maintaining the current baseline. Other medicines will be entitled to strengthened protection only if they can demonstrate no return on investment in view of investment costs, including for research and development.

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[114] Previously explored in the Joint Action on Antimicrobial Resistance and Healthcare Associated Infections.

[115] Baseline protection is the current regulatory protection of 8 years of data protection and 2 years of market protection which also applies in Option A; (new) standard protection is the regulatory protections of Options B and C of 6 years of data protection and 2 years of market protection.

Option B also encourages the development of novel **antimicrobials** that can fight resistant pathogens through a 'pay or play' model. Either a company holds an antimicrobial in its portfolio, or it pays into a fund for financing the development of novel antimicrobials. It also includes measures for prudent use of antimicrobials including monitoring consumption, optimising package sizes and stricter rules for the use and disposal of antimicrobials for human use and tightening of prescription requirements for example through the mandatory use of diagnostics prior to prescription of antimicrobials thus target pathogens better.

Access measures in Option B consist primarily of an obligation to launch centrally authorised medicines on the market in a majority of Member States (small markets included) within 5 years. If the obligation is not fulfilled, the medicine loses its protection, and generics can enter the market.

Measures on **security of supply** encourage EU coordination for exchange of information and use existing guidelines and systems, such as the EU medicines verification system[116] to track supply, and measures to increase manufacturers' responsibilities to ensure supply. The notification period for withdrawals remains identical to the baseline and MAHs are obliged to offer their MA for transfer to another MAH in case of withdrawals from the market.

The **ERA requirements** and conditions of use for medicines are strengthened. This option also foresees the assessment of the environmental risk of manufacturing in the ERA as part of the marketing authorisation. Moreover, it proposes improving oversight of sites through modification of rules on inspections and a mandatory joint audit scheme for national GMP and GDP inspectorates.

Non-pivotal elements in Option B include the possibility for regulators to impose a post-authorisation obligation for comparative studies on the effectiveness of a given medicine compared with the standard of care. Codification of rolling reviews beyond crisis-related medicines, and measures to future-proof the regulatory system by reviewing the scope and definition of products that need to be accommodated under the pharmaceutical legislation and simplifying/clarifying the regulatory framework for certain categories of medicines (e.g. borderline products) should facilitate innovation. Anti-competitive practices such as introducing multiple marketing authorisations are restricted, interchangeability of a biosimilar medicine with its originator medicine will be elaborated in the product assessment and the Bolar exemption (legal exemptions from patent infringements for acts relating to the regulatory submission of testing data) will be broadened to facilitate generic entry. Together with obligation for all MA applicants to publicly disclose any relevant public funding received (R&D **transparency**) this should address **affordability**.

5.2.4 Policy Option C

Option C proposes a 'quid pro quo approach' with a modulated system of **incentives combined with obligations**.

The regulatory protection for originator medicines in option C is split into a standard and a conditional period. The standard is 6 years data protection and 2 years market protection (as in option B) while the conditional period is 2 years (or 1 year, see box below with a variation of the option). The conditional year/years are granted only if the product is placed on all EU markets within 2 years of authorisation and appropriately and continuously supplied thus increasing **access** to patients. To be pragmatic, the provision has some exemptions (e.g. the possibility for a Member State to waive[117] the obligation within its territory for the purpose of the incentive). For it to be predictable for generic and biosimilar companies, a time limit is set (i.e. 2 years before the DP expires) for a final decision on the prolongation or not. If a company fails to comply with the market launch requirement, there will be earlier generic competition and increased **affordability for health**

[116] Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products, OJ L 174, 1.7.2011, p. 74.
[117] In the case that a MS does not wish to be supplied at that moment.

systems[118]. Moreover, originator medicines addressing an UMN would receive an additional 1 year of data protection to stimulate more innovation in areas of unmet patient need.

The system of special incentives in options A and C are similar but transparency on public contribution to the costs of clinical trials will be required for all medicines in option C. There is a special incentive (6 months) to stimulate developers to conduct comparative trials. **Incentives can be cumulated**, however the total regulatory protection period is **capped at 11 years**, which is a difference compared to Option A.

Variation to Option C

Option C aims at a balanced mix of obligations and incentives, which in individual cases may result in a higher level of protection for companies than the current baseline. To mitigate this result, a variation[119] to Option C is assessed, where no medicine could reach a 'beyond-baseline' level of protection. The variation consists of a reduction of the conditional **2 years** protection period to **1 year**, and a capping of cumulated incentives at 10 years.

The next sections will consider Option C with 2 years conditional period as default. The differences in impacts between the default option C and the variation are discussed in section 8.1.

Variation to Option C
6 years DP + **1 years DP if placed in all EU markets** +2 years MP
Special incentives:
+1 year DP for medicines that address UMN
+ 6 months DP for comparative trials
Incentives capped at 10 years.
Transferable exclusivity vouchers for antimicrobial products

With respect to **innovation**, the changes to the scope, definitions and classification advice with regard to medicines and the codification of rolling reviews and PRIME would be similar to option B. However, this option also foresees the inclusion of a sandbox environment (i.e. a structured form of testing before formal regulation) which would more readily accommodate innovation in breakthrough areas where the current framework does not sufficiently cater for this innovation. A binding system for scientific assessment of evidence for repurposing off-patent medicines will be established, and obligations will be simplified to facilitate non-commercial entities (e.g. academic) to become marketing authorisation holders. To incentivise development of novel **antimicrobials** that can fight resistant pathogens, a system of transferrable exclusivity vouchers (as in option A) is explored. The fight against AMR is corroborated with a strong emphasis on prudent use measures which are similar to those proposed in option B.

With respect to **security of supply**, in addition to an EU definition of shortages, critical shortages and critical medicines, option C measures include a balance of EU- and Member State-level actions to mitigate and prevent **shortages** and build on the shortage provisions in the EMA reinforced role legislation[120]. The approach to reporting shortages is harmonised across the EU, while monitoring of supply remains with Member States and only critical shortages are escalated to EU-level. As with option B, support to the management of shortages is increased through earlier, harmonised reporting on shortages. There is the possibility of information sharing by Member States on critical shortages and supply chain vulnerabilities.

The **ERA requirements** are similar to option B. It would also strengthen conditions of use of medicines on a case by case basis to limit the environmental impact without affecting the

[118] An alternative consequence could be repealing marketing authorisation of companies not launching in all EU, however this would deprive patients' access to the concerned medicine, hence this measure was discarded.

[119] During the evaluation several stakeholders from patients' groups and academia argued that incentives are overly generous within the EU.

[120] Regulation (EU) 2022/123 of the European Parliament and of the Council of 25 January 2022 on a reinforced role for the European Medicines Agency in crisis preparedness and management for medicinal products and medical devices, OJ L 20, 31.1.2022, p. 1.

appropriate therapeutic use. It will include AMR aspects in GMP to allow a more holistic assessment of environmental risk along the pharmaceutical lifecycle.

With regard to **non-pivotal elements**[121], this option foresees stronger oversight of manufacturing supply chains through changes to inspections, reinforced Member State inspection capacity (joint audits of inspectorates) and increased EMA coordination. The strengthened Bolar provision to promote competition and hence **affordability** listed in Option B is retained and the transparency obligation on public funding is limited to clinical trials. Improvements to the current Hospital Exemption will continue allow for the use of ATMPs without marketing authorisation, but under stricter conditions to ensure quality, safety and efficacy of these therapies.

Transferable exclusivity vouchers and r*estrictions on their granting and use*

The transferable exclusivity voucher is a tool to **generate funds for the development of novel antimicrobials**. The analysis in section 6.1.1.4 points to the conclusion that even though vouchers can be an expensive solution, they represent a credible measure against AMR if applied under strict conditions; their benefits and costs need to be weighed against the cost of inaction and the impact of AMR on health and economy[122].

By setting strict criteria for antimicrobials that can benefit from the voucher, its value would be calibrated to benefit the developer of the antimicrobial more than the buyer. The analysis in section 6.1.1.4 explains why vouchers can work only if they are very restricted to a limited number (i.e. max 1 per year). This is also the reason why they score differently in the impact assessment for orphan and paediatric medicines where such limitation is not possible (see details in Annex 4).

To achieve strict limitations, only those medicines that are 'game changing' antimicrobials for reducing AMR can receive '**novel antimicrobial' status** by the Agency, based on clear criteria set out in the legislation. The antimicrobial is considered novel, and thus eligible for the voucher if preclinical and clinical data underpin a significant clinical benefit with respect to antimicrobial resistance and it either represents a new class of antimicrobials or it has a new mechanism of action that is distinctly different from the mode of action of any authorised antimicrobial (criteria to be assessed by qualified experts). Moreover, the active substance should not have been previously authorised in a medicinal product in the EU that addresses a multi-drug resistant infection or a serious or life threatening infection. This will also direct investment and research into those game changing products. Even if found eligible, additional supply requirements, transparency conditions on funding received and on the sale or transfer of the voucher and other conditions will be set in the legislation.

There would be moreover a review clause in the legislation to evaluate the application of the vouchers after some years and decide on the continuation or not of the measure. It may take some time until an antimicrobial is authorised that is eligible for a voucher, a voucher may not be used immediately after it has been granted and the effect of the extension of data protection due to a voucher may also take some time to be seen. Several vouchers have to be granted and been used to gain sufficient experience for a review of the measure.

5.2.5 Horizontal measures

All options are complemented by a series of horizontal measures. These are necessary to improve the effectiveness and efficiency of the regulatory system overall and will act on core elements of the authorisation and lifecycle procedures. They respond to the specific objectives of **innovation**, and **reducing the regulatory burden and providing a flexible regulatory framework**.

Generic marketing authorisations will be simplified by enabling a common assessment of manufacturing data across products, as generic medicines often source active substances from the

[121] See Annex 11 for details.
[122] AMR-Tackling-the-Burden-in-the-EU-OECD-ECDC-Briefing-Note-2019.Pdf

same site. A more efficient repeat use procedure[123] will be provided to reduce administrative and cost/burden and prevent medicine shortages. Furthermore, the sunset clause and renewal of MAs after five years will be abolished to simplify procedures. Likewise, the envisaged reduction in the number of notifiable variations reduces the administrative costs incurred by MAHs and regulators.

Provisions of the legislation will be reviewed with regard to novel combined products (e.g. where medicines are coupled with medical devices, software, or artificial intelligence). To address shortcomings highlighted in the evaluation[124] the legislation will ensure complementarity with the medical devices regulation/in vitro diagnostic regulation in relation to benefit/risk assessment, responsibilities of the medicine developer, and joint scientific advice.

In addition, delinking the environmental risk assessment of medicines that contain or consist of GMOs from the GMO legislation and replace it with GMO environmental risk assessment requirements and procedures adapted to the specificity of medicines under the general pharmaceutical legislation is considered, but these changes would not constitute a complete derogation from the GMO legislation.

New concepts will be integrated, such as adaptive clinical trials and full use of health data (real world evidence), applying the digital by default principle, notably through electronic submissions of applications, variations to MAs and electronic product information. The provision of authorised electronic product information for EU medicinal products would enable easier access to data contained within the product information, taking into account needs of patients, consumers and healthcare professionals, as well as the risk of digital exclusion.

The working methods of EMA and the European medicines regulatory network will be adapted, especially with regard to the functioning of the centralised procedure and the decentralised procedures, the use of expert assessment teams and multi-expert inspections teams to ensure a better use of the available network resources. The evaluation also identified suboptimal coordination between the EMA committees that duplicate work, create administrative burden and risking delays especially in the assessment of medicines for rare diseases and for children[125] and ATMPs. An EU-wide centrally coordinated process will be foreseen offering early dialogue and more coordination among clinical trial, marketing authorisation, health technology assessment bodies and pricing and reimbursement authorities for integrated medicines development and post-authorisation monitoring, pricing and reimbursement.

6 WHAT ARE THE IMPACTS OF THE POLICY OPTIONS?

6.1 Economic impacts

The general pharmaceutical legislation rewards innovators through the **regulatory data and market protection (RP)**. By protecting data on the safety and efficacy of the product, RP guarantees that during the data protection period no generic/biosimilar medicine can obtain a marketing authorisation referring to the originator's data. This effectively protects innovators from generic or biosimilar competition[126] for 10 or 11[127] years after authorisation. In comparison with other jurisdictions, the EU ranks high (see **Table 2)**.

[123] See glossary.
[124] See Annex 5. The evaluation showed the need for more clarity on roles and responsibilities and for a more integrated approach in relation to scientific advice on medicines and medical devices.
[125] SWD(2020) 163 final.
[126] RP does not prevent companies willing to undertake their own clinical testing to seek marketing authorisation for the same medicinal product if they do not infringe on any patents or SPCs. However, that would be rather costly for entering a market, where the originator medicine is already present, and hence rarely occurs.
[127] An extra year is granted for an additional indication with significant clinical benefit. Historically around 1 in 8 medicines qualify for that.

Table 2 Basic regulatory protection periods for medicines globally[128]

Country	Protection	Duration
Canada	New Chemical Entity+ Market Protection	6+2 years
EU	New Chemical Entity+ Market Protection	8+2+1 years
Switzerland	New Chemical Entity	10 years
USA	New Chemical Entity (small molecule)	5 years
USA	Biosimilar Application Approval Exclusivity (biologic)	4+8 years
Israel	Market Protection	6 or 6.5 years
China	New Chemical Entity	6 years
Japan	New Chemical Entity	8 years

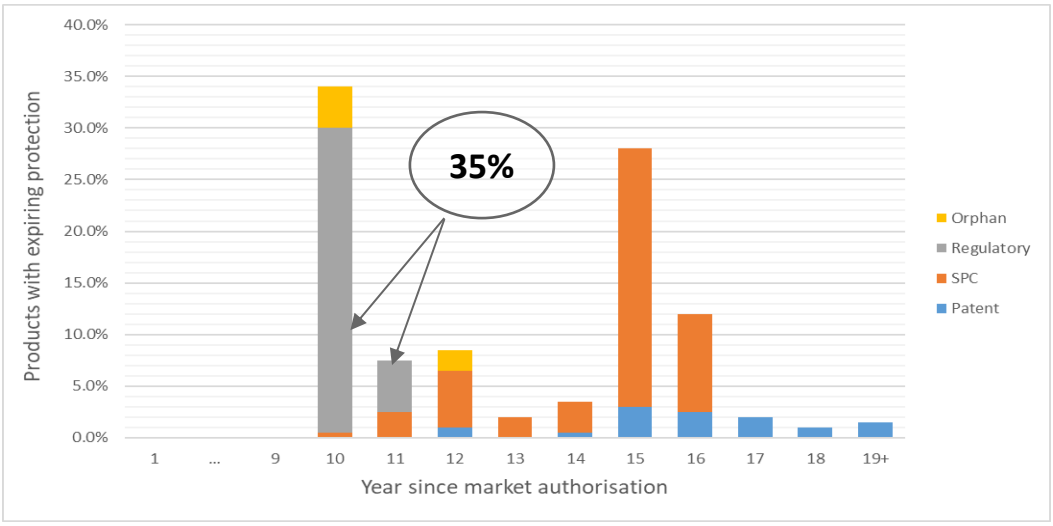
In addition to RP, medicines are also protected by patents (20 years), SPCs (up to 5 year extension of primary patent, but maximum 15 years from marketing authorisation), and medicines for rare diseases also benefit from 10 years market exclusivity (+2 years if paediatric studies were carried out)[129]. The patent and SPC protection start from the patent filing, and depending on the time until authorisation they may offer longer or shorter protection than RP. It differs case by case which instrument provides the longest protection period after entering the market, as demonstrated by **Figure 3** on a representative sample of 200 medicines. Medicines protected by patent or SPC not only enjoy a longer protection, but on average they generate 2-3 times higher revenues than those protected only by RP (Table 3).

Table 3 Medicines' protection period and revenues by their last layer of protection

Last line of protection	Number of products	Avg. protection duration	Avg peak annual sales[1]
Regulatory protection	69	10.1 years	**€ 158.7 m**
Market Exclusivity	12	10.7 years	**€ 41.7 m**
SPC	95	14.3 years	**€ 368.3 m**
Patent	23	16.7 years	**€ 300.5 m**
Grand Total	**199**	**12.9 years**	**€ 268.2 m**

We expect this ratio among protection types to remain in the next 15 years, therefore the changes to the RP would **concern around 1/3 (i.e. 35%) of the new medicines**, which have a **23% share among all originator medicine sales in the EU**.

Figure 3 – Ratio of medicines by the length of last layer of protection and type of protection

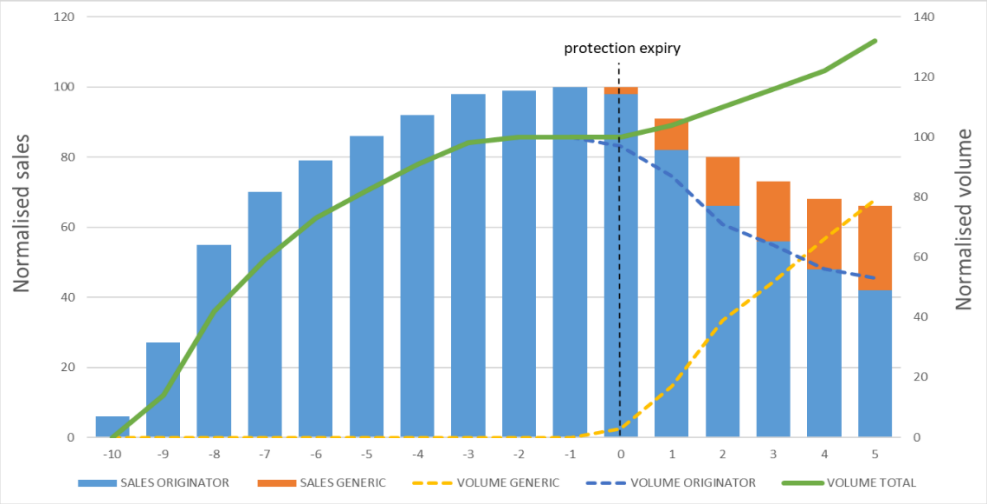


We provide a conceptual model to explain the economic impacts of the changes in the RP, on the different stakeholders. The model is based on the commercial lifecycle of a representative innovative

[128] Data collection by Technopolis Group, 2022.
[129] A diagram with the current regulatory and IP protections in the EU can be found in Annex 9.

medicine, an analogue, for which RP is the ultimate protection. To create this analogue, historical data[130] were examined, and the evolution of sales followed from market authorisation until protection expiry, and 5 more years from then, along with generic/biosimilar sales, **Figure 4**. The model uses normalised units to represent prices and volumes across different products, where 100 is equal to originator's peak sales, at year -1. It is assumed that the pricing strategy of the manufacturers remain unchanged. The calculations were done based on the public, list prices (not the actual, confidential prices).

Figure 4 Normalised sales and volume for products with 8+2 years of RP protection (baseline)



The SPC evaluation[131] highlighted that generic competition is not uniform across medicines. High-sales medicines, small molecule medicines are more likely to be contested and by more competitors, leading to quick erosion of the price and the innovator's premium. On the other hand, biological medicines, medicines for rare diseases and low revenue products are less likely to be contested, resulting in slower price erosion, or even maintaining a monopoly position. To account for this variability, the model considers the average evolution of sales volumes and values across all the RP-protected medicines in a nine-year cohort, including those medicines that were not contested by generics after protection expiry. The model represents well real-life at systemic level, even though some medicines – for example, those that face a high number of competitors – might show a much steeper erosion, whereas others might see persistently high sales after expiry in the absence of competitors.

From year 0, the generic medicines enter the market with a lower price, carve out a growing market share and force the originator to offer discounts[132]. The volume of generic medicines steeply increases, partly because some users substitute the originator medicine with generics and partly because the total volume rises with increased affordability. For health systems, the price drop following generic competition means cost savings. In our analogue, the price drop is 50% on average at year +5. The lower price extends eligibility and more patients and from more Member States can have access to the medicine either in its original or generic form. Even with the 32% more patients served at year +5, health systems pay 34% less than at peak sales in year -1.

To account for the impacts of modifying the RP, we use the above baseline and the 16 years observation period, which we consider as the commercial lifetime of an RP protected medicine. This allows to understand how the stakeholders' positions change under the different scenarios. Extending the protection allows innovators to seek longer monopoly rents, but it delays cost savings

[130] A cohort of medicines approved between 2004 and 2011, where RP is the last defence. Further explanation of the inputs used for the model is provided in Annex 4.
[131] SWD(2020) 292 final.
[132] The evaluation (Annex 5) found that originator products can maintain a 30% premium over their generic competitors.

and broader access for the public and delays revenues for generic companies. Decreasing protection has the exact reverse effect.

Profit, sales, cost, volumes – how we measure economic impacts for key stakeholders

For **health payers** we measure the impact of changes by the change in the **cost of medicines**, which can be directly deducted from total sales of originator and generic medicines in IQVIA data.

For **patients**, we measure the impact of change by the change in the **volume of medicines**. The more the volume, the more patients could benefit from therapy, either using originator or generic product. We will indicate the monetary value of the volume difference as "Δ of patients treated (monetised)".

For **originator** and **generic industry** the key measure of impact is **the profit** that they can realise from their business operations.

There is no readily available dataset on profits but we have good data on sales (revenues) from the IQVIA database. By deducting the cost of sales from the revenues, we can calculate the gross profit. The gross profit only includes the variable costs of manufacturing and distribution, but not the fixed costs, such as R&D and investment in infrastructure. In our model we distinguish three categories of revenues, each with a different margin of gross profits.

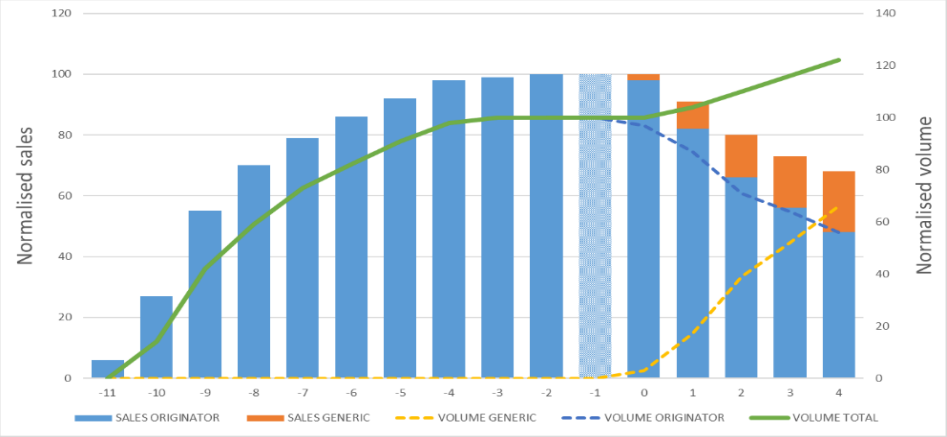
- **Protected originator sales**: this is the most profitable category during the protected period of new medicines. Based on a sample of reports from publicly listed companies we apply a 80% gross profit margin on the revenues (20% cost of sales)
- **Contested originator sales**: once generics enter the market, originator products are forced into price competition. Still, originator products can maintain a price premium compared to generics albeit reduced thanks to brand loyalty and strong sales force. We assume a 50% gross profit margin in this category.
- **Generic sales**: generic industry operates on a high volume, low margin basis. With low product development risk, a lower profit margin can be sustainable. We apply a 33% gross profit margin on generic revenues.

6.1.1 Economic impacts of key policy measures

6.1.1.1 Special incentives through increasing regulatory protection (Option A and C)

To understand the economic impact of an increased regulatory protection (either offered for UMN, comparative trials or market launch) we have added an extra year of protected sales to our model, and analysed the gains/losses for the different stakeholders during the observed 16 years (**Figure 5**).

Figure 5 - Normalised sales and volume for products with 8+2+1 years of RP protection



The longer protection translates into higher profits for the innovator but increases the costs for patients and payers, and also delays revenues for generic manufacturers. Overall, payers, patients and the generic industry share the burden of allowing longer streams of monopoly revenues to the innovator, to compensate for extra costs occurred (comparative trial, market launch), or to reward and incentivise innovation of high public health benefit (UMN). The exact monetary impact depends on the length of additional protection, and on the number of medicines expected to benefit from a certain incentive. Below we assess the special incentives one by one.

Special incentive: 1 year extension of RP for medicines addressing UMN (Option A, C)

This measure affects RP protected medicines as last protection, altogether 35% of all new medicines. Of these we expect 15-20% to address UMN. Applying these rates on the 45 annual new authorised

medicines as per our dynamic baseline, **on average 3 special UMN incentives per year are expected**. It is worth noting that for orphan medicines too an incentive for high unmet medical needs is foreseen, extending the market exclusivity period beyond the modulated RP protection for those orphan medicines.

Table 4 – Impact of change of +1 year regulatory protection for UMN

1 year increase in RP	Product level change	Systemic change (3 medicines)
Originator gross profit	**+€94m**	**+€282m**
Generic gross profit	-€13m	-€39m
Cost to public payer	+€54m	+€162m
Patients monetised gains/losses	-€28m	-€84m
Patients + payer monetised gain/loss	**-€82m**	**-€246m**

Table 4 summarises the monetary gains and losses of the different stakeholders at a single product level, and also at systemic level, counting with 3 incentives a year. For affected medicines, the **innovators'** gross profit will increase by €282m a year, and the incentives would increase the cost for payers by €162m. Taking into account that some patients will not have access to the medicine due to the sustained higher price, the total **cost will be €246m to the public**.

In exchange for this public cost, the UMN incentive would directly reward investment in UMN R&D and likely would have a spill-over effect: national and EU-level research and innovation funding could be specifically channelled to UMN, and national pricing and reimbursement systems could differentiate the UMN addressing medicines, making them even more viable commercially.

We expect that the incentive would attract more investment in UMN and **result in 1-2 additional UMN medicines per year**, for the benefit of the patients and creating savings for the health systems. This important and non-monetised[133] benefit has to be seen together with the costs.

The consultations showed that both public authorities and patients support modulating the RP periods around factors such as UMN. Industry on the other hand said that if incentives were limited to UMN only, that would disregard the reality of science and incremental innovation and would introduce uncertainty for businesses as the ultimate duration of the regulatory protection period would not be fully clear when their investment decision is made[134].

Special incentive: 6 month RP extension for comparative clinical trials (Option A, C)

Similar to the previous incentive, this measure could benefit medicines for which RP is the last layer of protection, making around **35% of all new medicines eligible**. Conducting comparative trials may not be feasible for some medicines, and if the cost of the comparative trial is too high as opposed to the reward, companies will decide to decline the incentive. Taking these factors into account, we expect that half of the RP products or **8 medicines annually** could benefit from the incentive. Table 5 shows the economic impacts on the main stakeholder groups of this incentive both at individual product level and at systemic level, for the 8 medicines per year.

Table 5 – Impact of change of +6 months year regulatory protection for comparative trials

6-month increase in RP	Product level change	Systemic change (8 medicines)
Originator gross profit	**+€47m**	**+€378m**
Cost of comparative trial for originator	**+€35m**	**+€280m**
Generic gross profit	-€6.5m	-€52m
Cost to public payer	+€27m	+€218m
Δ of patients treated (monetised)	-€14m	-€112m

[133] Monetising the benefits of an additional new medicine has several challenges: there is a large variation between medicines' value, defined by the patient population and severity of disease. Moreover, monetising a medicine's value requires putting a monetary value on patients' life and health, as well as on the physical and emotional burden of their families and carers. We thus have chosen not to monetise these impacts, but quantify them as much as possible.
[134] See Annex 14 for further details on the factors influencing access and affordability.

Patients + payer monetised gain/loss	**-€41m**	**-€328m**

Comparative clinical trials have a cost. In the absence of publicly available data, we estimate the cost of a comparative clinical trial at €20-50m (the model uses the middle value of the range), referring to the paediatric trials as a benchmark[135]. Due to the revenue extending nature of the incentive, higher sales medicines would have a higher compensation, independent from the cost of the trial.

For the public, 8 trials a year would cost €328m, but at the same time it would generate important non-monetised benefits: comparative trial data will enable public authorities making better informed reimbursement decisions and saving cost down the line. Data from trials would also accelerate pricing and reimbursement decisions, allowing faster access to patients.

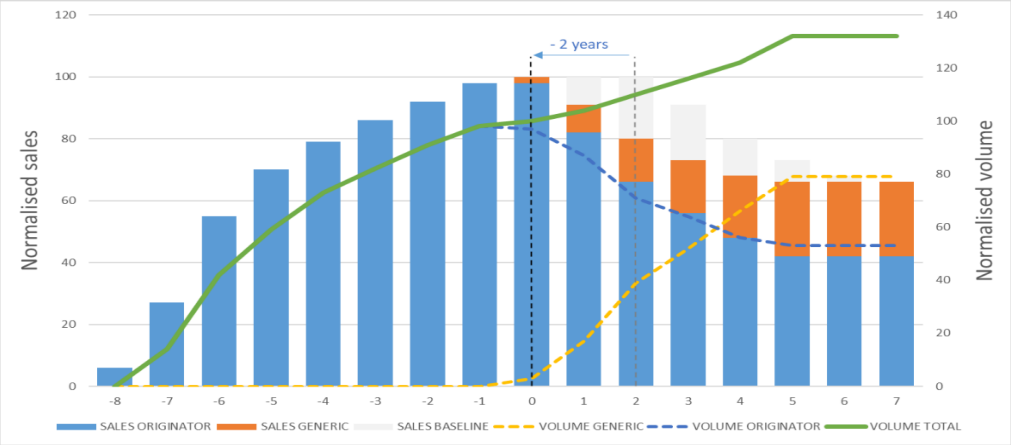
In the consultations, industry stated that comparative data is already provided at authorisation stage when possible and that some products (e.g. ATMPs, products for ultra-rare diseases) will not benefit from this incentive. Patients and public authorities on the other hand supported comparative clinical trials (even as an obligation in the case of the latter).

6.1.1.2 Decreasing standard regulatory protection (Option B)

A key feature to support affordability in Option B[136] is a decreased regulatory protection, from 8+2 years in the baseline to 6+2 years, except for a minority of medicines: UMN addressing medicines and medicines with no return on investment can maintain 8+2 years RP.

To model for the change, we removed from our analogue the original year -1 and -2, enabling earlier generic competition. To keep the same 16 years of observation period, we have added year +6 and +7 in the model, which we assumed to be equal to year +5[137] (**Figure 6)**.

Figure 6 - Normalised sales and volume for products with 6+2 years of RP protection



This measure would only concern medicines that have RP as the last layer of protection, about 1/3 of the 45 new medicines. Out of this 15 medicines, 20% may be UMN addressing or low revenue thus exempted from the measure. Some of the RP protected medicines are eligible for SPC protection between year 8 and 10 from market authorisation, partially offsetting the RP reduction. Overall, **9-12 medicines may be affected** by the reduction annually. **Table 6** summarises the impacts at product and systemic level for the different stakeholders.

Table 6 – changes between baseline and RP 6+2 per stakeholder

2 year decrease in RP	Product level change	% change	Systemic change (9-12 medicines)

[135] The joint evaluation of the orphan and paediatric regulation estimates the cost of paediatric studies at €22m.
[136] This section discusses Option B solely, the eventual loss of protection in Option C for some medicines not complying with the access condition is discussed in 6.1.1.3.
[137] More on the assumptions in Annex 4.

Originator gross profit	-€188m	**-15%**	**-€1.97 b**
Generic gross profit	+€25m	+56%	**+€266 m**
Cost to public payer	-€107m	-6%	**-€1.13 b**
Δ of patients treated (monetised)	+€71m	+5%	+€745 m
Patients + payer monetised gain/loss	+€178m	+9%	**+€1.86 b**

Compared to the baseline, affected **originators** would lose their two highest-revenue, most-profitable years. The product would **lose 15% of its lifetime profits**. For the originators this sums up to €2bn loss annually in gross profits from the EU. More than 75% of originators replying to the targeted survey expressed a negative stance towards a reduction of protection period for products that do not address an UMN.

On the other end, the measure would generate €266m additional gross profit for the generic industry, and €1.13bn direct cost reduction for health payers. Thanks to the lower price, 5% more patients could benefit from the concerned medicines and accounting for the extra patients served in a monetised form, the total benefit for the public is €1.86bn, or 0.9% of the total EU pharmaceutical expenditure. An additional benefit would be a higher proportion of UMN among newly approved medicines, due to the relative higher reward.

Because of all the other co-existing protections (SPC, patent, market exclusivity), option B **would leave 75-80% of new medicines unaffected. The saving for payers and patients, would be borne by a dozen of medicines, which would lose 15% of their profits.**

Apart from the imbalanced impact, the measure would have additional costs. With a lower reward, some developers may decide not to enter the EU market, or delay entry and seek return on other markets first. An estimated **€670m will be lost for innovation**[138] that could benefit patients.

Even though in the consultation civil society organisations in principle supported a reduction of regulatory protection, patients would pay the highest price for the lost innovation, in that their medical needs could not be met. Innovation is important for health payers too if new products offer cost-effective health solutions, and a continuous stream of innovative medicines is needed for the generics industry for new business opportunities.

Would the RP reduction harm EU competitiveness?

A direct link between EU incentives and EU competitiveness is hard to establish because while the incentives make the EU markets more attractive, they are agnostic to the medicines' geographical origin. Around 20% of new medicines authorised in the EU are from the EU, the others are mainly from US, UK, Switzerland and Japan that are equally eligible to all EU incentives. Equally EU based innovative companies can benefit from incentives elsewhere, if they sell their products there.

In June 2016, the Council requested the Commission to conduct an evidence-based analysis of the impact of incentive mechanisms, notably SPCs. Two studies have been commissioned. One from Max Planck Institute[139] questions whether the availability of patent or SPC protection affects companies' decisions to locate research facilities in one jurisdiction or another, emphasising that other factors are likely of greater importance. The Copenhagen Economics study[140] argued that SPCs could play a role in attracting innovation to Europe, pointing out that taxation, education, and other factors are probably more significant in that respect.

[138] 20% of lost protected sales, the typical R&D rate of revenue for originator companies, calculated in Annex 4.
[139] Max Planck Institute. Study on the legal aspects of supplementary protection certificates in the EU, 2018.
[140] Copenhagen Economics. Study of the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards, 2018.

6.1.1.3 Measures to improve market access (Option A, B and C)

All policy options address the challenge of unequal market access to new medicines across the EU but with different measures. As all options modulate RP, they all would impact those medicines that have RP as the last layer of protection, 35% of new medicines, **15-16 medicines a year**. Option A offers a +6 months RP extension incentive for medicines launched in all EU markets within 5 years of authorisation. Option B instead requires companies to launch their product in the majority of all EU countries within 5 years, otherwise they lose their protection and generics are allowed to the market. Option C requires market launch in all EU MS (except those not interested in the product) within 2 years of authorisation as a conditionality to parts of the protection period. Complying medicines would gain 2 years of conditional RP (or 1 year in the case of the variation of Option C).

We have also observed a strong correlation between a medicine's peak sales and its access across EU countries. The magnitude of the incentive or the loss of protection is commensurate to the peak sales, meaning that for high sales medicines the motivation is very high to comply. Since high-sales medicines are launched already in most of the markets, for them the compliance cost is small. The opposite is true for low sales medicines.

Based on the size of the incentive (or potential loss in option B and C), the compliance is estimated as the percentage of medicines fulfilling the market launch requirements. From this, the costs or savings to the public have been calculated (**Table 7**). For option A, we used the same model as for the special incentive for comparative trials, but expecting that only the higher sales medicines would comply, a higher average peak sales was used in the model (detailed in Annex 4).

In option B and C the concept is reversed. If a medicine complies with the requirements, the stakeholders' position do not change. But non-complying medicines would face earlier generic competition, resulting in losses for originators and in gains for the public and generics. To calculate public savings stemming from non-complying medicines we used the model of the decreasing standard regulatory protection (section 6.1.1.2). Again, the average peak-sales value was adjusted, assuming that the low-sales medicines will be the ones not complying.

Table 7 – Comparative table of measures improving access

Option	Expected compliance	Originator's reward/loss	Cost/benefit for public
Option A +6 months, if in all EU	50% (6-8 medicines)	+€527 m gross profit +7.5% gross profit for 7 complying medicines	+€455 m public cost
Option B -5 years, if not in majority of MS	75% (11-13 medicines) Majority of markets	-€842 m gross profit -34% gross profit for 4 non-complying medicines	€681 m gain from non-complying medicines
Option C* -2 years, if not in all EU	66% (10-12 medicines)	-€469 m gross profit -15% gross profit for 5 non-complying medicines	€444 m gain from non-complying medicines

* The differences in impacts between the default option C and its variation are discussed in section 8.1

To determine compliance we use assumptions and this inevitably carries uncertainties. Originator industry is better off with higher compliance and worse off with low compliance, which then results in profit losses. For the public, high compliance is the desired outcome, resulting in faster and increased access. However, non-compliance lowers the cost by shortening the protection period and thus contributes to affordability, also an improved outcome compared to the baseline.

The access measures benefit society, above all patients. These benefits are elaborated in the social impacts section (6.2). Option B has the disadvantage that it is unpredictable. Until reaching 5 years on the market, the generic industry will not know for sure whether the originator medicine complies or not. If generic companies prepare for non-compliance, and start development and production, the innovator's compliance would delay their entry by 3 years. And in case of non-compliance without the generic companies being prepared, there will be no generic competition for quite some time, neutralising part of the expected impact of the measure.

Practical details and impact of modulation of data protection for market launch (option C)

The access conditionality would be a first-of-its-kind policy measure that addresses a problem specific to the EU, and the primordial goal of it is to increase and accelerate EU patients' access to new medicines, regardless of the country they reside. The measure is successful if it is widely used and a high proportion of new MAHs comply with the requirements and benefit from the incentive. A low success rate would discourage companies and would not achieve access in all Member States.

Lack of access in a particular Member State can have many reasons. Sometimes companies decide not to launch or delay launch in a market because of low profitability, small patient populations, perceived cumbersome procedures, pricing policy, parallel trade. In other cases, Member States deny access because no therapeutic value is seen, the medicine is not cost-effective according their HTA assessment, or it would have an unbearable budget impact. There may also be objective roadblocks, such as the need for highly specialised delivery infrastructure or diagnostic tools for the therapy that do not exist in the Member State.

The proposed measure in option C targets companies to do their utmost to launch the medicine in all EU markets within a specific period after authorisation (e.g. 2 years) and ensure a continuous supply. This includes that companies shall file for pricing and reimbursement in all 27 Member States, they have to conduct negotiations in good faith, and upon positive decision ensure supply that covers the Member States' needs[141]. However, companies could still receive the market launch incentive if due to reasons beyond their control the market launch is delayed or not happened at all (e.g. the Member State doesn't wish to be supplied at that particular moment or doesn't have the specialised infrastructure e.g. in case of orphan medicines or ATMPs).

The Commission would grant the extra protection (2 years or 1 year for the variation to option C) based on a system where Member States will be obliged to confirm within a certain period after marketing authorisation compliance with the conditions of the incentive, justify a refusal by a statement of reasons based on objective and verifiable criteria or give a waiver to the company. Non reaction of a Member State will be considered as tacit confirmation of compliance.

Companies should not find it difficult to comply with the conditions of this incentive, as EFPIA already made a voluntary commitment[142]: their members would file for pricing and reimbursement in all EU27 Member States within 2 years from authorisation. This is already a step forward from the current situation, but it is voluntary, restricted to EFPIA members and there are no controls in the system. Hence, it does not work to the extent of the incentive, which relates to actual launch and supply not just filing. The proposed measure adds a significant financial incentive for complying, and it can also prevent dishonest applications[143]. By making ignoring certain markets or abusive negotiating practices very expensive, Member States, and especially smaller Member States would have a more balanced position when dealing with global firms.

The instrument to work adequately would also require Member States to act timely and in good faith, because if compliance is made unduly difficult and unpredictable, the access goals will not be met. Considering the common goal of both industry and Member States to ensure wide patient access in the EU, we expect this change to contribute positively to the negotiations between the two parties and that blocking the incentive will indeed be reserved to the objectively justified situations. Ultimately, any alleged abusive behaviour can be subject to judicial control at Member State level and a revision clause could be built in to take stock of performance after a certain time.

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[141] The Transparency Directive allows 180 days for Member States to make their pricing and reimbursement decision, therefore filing at 18 months shall allow a market launch in 2 years.

[142] EFPIA Access to medicines (efpia.eu)

[143] We have seen examples in the past that a small member state was offered 4-6 times higher price than Germany.

The specific situation of **SMEs and not-for-profit entities** and their capacity to engage in multiple parallel pricing negotiations will be taken into account by allowing longer period to comply with the market launch conditions, **3 years from authorisation**.

We can expect this measure to spur a **long term behavioural change** of both industry and public actors to engage more towards increasing access, which is a strong demand from public authorities and citizens. Ideally, launching new medicines in all 27 Member States in a timely fashion would be the standard for all medicines, and not only for the 35% of them (with RP as the last layer of protection) that are directly affected by the incentive.

Such incentive has not yet been tested on the market, however stakeholders were willing to share their views about it. Public authorities in the targeted survey and a workshop were overall positive to linking incentives with market launch, while industry was against. For industry, access depends on factors that are not under their control (e.g. variations in national reimbursement decisions); however, they agreed that the measure can be a financial incentive to launch in smaller markets. To address this concern, the design of the measure includes the safeguards explained above. Civil society organisations, patients, researchers and public authorities considered this measure as very important. They stressed the need to provide 'real' effective access and continuous supplies. Some public authorities argued that this measure should be an obligation. Member States have highlighted in a series of Council conclusions[144] that incentives need to be proportionate to the goal of encouraging innovation while improving patients' access to innovative medicines. They considered that deferred or missed market launches, and business behaviour, including high priced essential medicines pose a high burden for patients and health systems. They called the Commission to evaluate the system and take action.

Would a decreased protection translate into price increase?

Companies may try to increase prices to compensate for a shorter RP if they do not get the incentive, however, this will result in lower volumes sold, less Member States and fewer patients could afford the increased price. Rationally behaving companies should not have different pricing policies because of the length of protection, a higher price does not automatically lead to higher profits[145].

The Evaluation[146] compared prices of the top-selling almost 200 medicines in the EU, US, Australia, Canada, Japan and Switzerland. **We could not find any correlation between the prices and data protection periods**, however in the US prices for the same medicines are often 3-5 times higher than in other countries despite offering very long effective protection[147].

6.1.1.4 Measures addressing AMR (Options A, B, C)

Annex 15 describes innovative financing solutions – outside of the general pharmaceutical legislation – introduced in some EU Member States and some international initiatives to incentivise development of new antimicrobials.

Pay or play model (Option B)

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[144] Council conclusions on strengthening the balance in the pharmaceutical systems in the EU and its Member Stateshttps://www.consilium.europa.eu/en/press/press-releases/2016/06/17/epsco-conclusions-balance-pharmaceutical-system/; Council conclusions on innovation for the benefit of patients: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52014XG1206(03)&from=SK; Conclusions on strengthening the European Health Union: https://data.consilium.europa.eu/doc/document/ST-14029-2021-INIT/en/pdf

[145] A recent and extreme example is the case of Zynteglo®, a gene therapy authorised in the EU in 2019. The company insisted on a high price (more than €1m) that not even the richest markets were willing to pay, and led to zero sales and zero profits in the EU market.

[146] Notably the indicator AFF-1.2 on p100 of Annex 10, Analytical report.

[147] On the other hand, more new medicines and much faster than in the EU are made available to US patients, at least for those who can afford a premium insurance scheme.

In this model, a company co-finances the innovation and either holds an antimicrobial in its portfolio or it pays to a fund to finance the development of novel antimicrobials. A recent analysis[148] found that a pay or play model would impose additional costs on EU pharmaceutical businesses with the risk that the costs would be passed on to health systems (insurers and/or patients) through higher prices and while a minority may look to avoid a levy by developing antimicrobials or acquire businesses with an antimicrobial in the portfolio, the majority would likely view the surcharge as an unavoidable cost to be factored into their wider pricing policies. In addition, the fund would generate only limited amount of money so that only a limited number of rewards can be ensured. The results of this model could be seen only after several years (when the fund collects enough capital).

The pay or play model would not directly increase the number of novel antimicrobials and may increase prices of other medicines, creating substantial social costs. The benefits of the incentive would depend on the use of the collective fund, which is beyond the scope of the general pharmaceutical legislation.

This measure was supported by patients and other civil society organisations in the public consultation. Industry was the least supportive, they raised concerns that the model would unfairly penalise companies (particularly SMEs) with no expertise in AMR product development.

Transferable exclusivity vouchers for novel antimicrobials (Options A and C)

These would benefit in particular SMEs as they would be rewarded as early as regulatory approval for a new antimicrobial. It would also increase the attractiveness of the field for private financing mechanisms, such as venture capital. According to EFPIA[149], the value of such voucher in the EU should be between €280 m and €440 m per product, based on assumptions around a "fair European share", a proportionate contribution of the EU towards the development of a novel antimicrobial product that would benefit the global population. The voucher could be an important part of the EU response to AMR for the **development of novel antimicrobials**, i.e. not just products that are already in the (weak) pipeline. Such response could also include other initiatives, outside the legislation, such as joint procurement for antimicrobials under HERA to **guarantee revenue** paid to producers **for ensuring access** to existing or new antimicrobials.

Cost and benefit of transferable exclusivity vouchers

To understand the impacts of a voucher, the model of RP extension has been used, with some adjustments. The buyers and thus users of the vouchers would be companies that hold the products with the highest sales among the RP protected medicines. The commercial lifecycle of these products differs from the average, as their market is more attractive for generics/biosimilars. It results in a faster erosion of price and sales, therefore an additional year of protection has a higher value for the originator, and a higher cost for the other stakeholders. We have examined over a 10-year period the highest selling RP protected medicines, and identified the champions for each year. We used in our model a €545 m average peak annual sales for these champions (More details on the model in Annex 4). **Table 8** summarises the effects to the various stakeholders.

Table 8 – Changes to baseline with the voucher and value of voucher

Stakeholder	change	change %
Originator gross profit	**+€387 m**	+10.1%
Generic gross profit	**-€54 m**	-23%
Cost to public payer	**+€283 m**	+4.7%
Patients monetised gain/loss	-€158 m	-3.8%
Patient + payer monetised gain/loss	-€441 m	-7.3%

[148] (https://academic.oup.com/cid/article/71/8/1994/5736365?login=true).

[149] Representative of innovative industry: A new EU pull incentive to address Anti-microbial Resistabce (AMR) Recommendations from EFPIA.

The €545m gain of the originator in protected sales is not equal to the value of the voucher for the originator, because the revenue contains the cost of manufacturing and distribution, as well as the cost of capital. We assume that the originator can only use the voucher 2 years after buying it, to ensure that generic competitors can prepare for a delayed entry. Assuming 20% cost of sales and 10% annual cost of capital over 2 years, the **value of the voucher for the originator is € 360m** at a **cost of € 441m for payers and patients** (or €283m in nominal value, disregarding patients' loss).

Sharing the value of the voucher between buyer and seller

We were able to identify the likely average value of the voucher, however it remains uncertain what proportion of the value will be transferred to the seller – the actual developer of the rewarded antimicrobial, often an SME. The negotiating position of the seller will depend on the second highest selling medicine, the next potential buyer, similar to an auction where the winner has to pay only a little more than the second highest bidder. The situation is further complicated if there are more vouchers on the market and the EFPIA paper estimates 1-3 vouchers per year. Each additional voucher drives down the price for all vouchers in that year, as they generate competition for each other. For instance, if there are 3 vouchers, the price for all will fall between the value of the voucher for the 3rd and 4th best seller medicine. Using historic data on the second, third and fourth best-selling RP protected medicines in a given year, we can visualise the impact. (**Figure 7, Table 9**).

Figure 7 Distribution of buyer and seller advantage if 1 or 3 vouchers issued a year

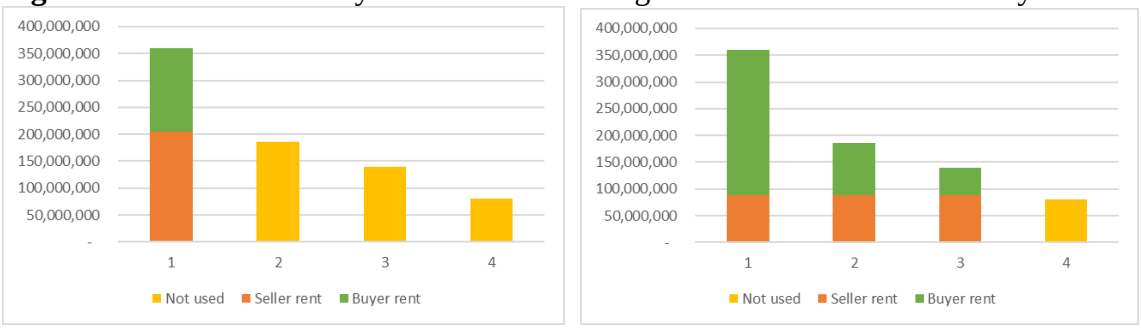


Table 9 – share of value among buyer, seller and the public

1 voucher		**3 vouchers**	Voucher 1	Voucher 2	Voucher 3	Total
Seller rent	**€205 m**	Seller rent	€89 m	€89 m	€89 m	**€267 m**
Buyer rent	**€154 m**	Buyer rent	€270 m	€97 m	€50 m	**€417 m**
Cost to public in nominal value	**€283 m**	Cost to public in nominal value	€283 m	€147 m	€109 m	**€539 m**
Cost to public incl. unserved patients	**€441 m**	Cost to public incl. unserved patients	€441 m	€228 m	€170 m	**€839 m**

In the model, based on historic sales data, **the buyer captures 43% of the voucher's value** if there is one voucher per year, and 61% if there are three vouchers annually. The buyer's share is sensitive to the gap in the voucher's value between one buyer and the next. The smaller the gap, the higher proportion of the value remains with the developer (seller). Appropriate safeguards and modulation of the voucher system could potentially improve the buyer/seller value-sharing ratio.

The voucher not only generously rewards the buyer without merits, but the public has to pay a high price to the developer. We present the cost for the public payer to reward the developer with 1€ in **Table 10** both in nominal value (the net budgetary effect for payers) and with a cost that takes into account the lost volumes and thus unserved patients.

Table 10 - cost for the public payer to reward the developer with 1€

Scenario	1 voucher	2 vouchers	3 vouchers
Cost to public in nominal value	**1.38 €**	**1.40 €**	**2.02 €**
Cost to public incl. unserved patients	**2.15 €**	**2.18 €**	**3.14 €**

If it were possible to add safeguards, ensuring that 90% of the value of the voucher is captured by the seller (developer), the ratio of the award and the cost would significantly improve. In this case, it would cost €87 m to the health payers to give a €100 m reward, but this payer cost does not account for the unserved patients' loss[150].

Regardless of the cost calculation method, the public has to pay more than 1€ for each euro awarded to the developer. However, it would be a feasible way **to pool sizeable resources and incentivise antibiotic development,** which so far have proven ineffective with other incentives. These costs should be put on balance with the current **€1.5bn in health care costs and productivity losses from AMR**[151] and the risk from the high levels of antimicrobial resistance in bacteria from human infections, a silent pandemic that is not subsiding, and its economic consequences. Benefits are further detailed in the social impact section (6.2).

In the consultations, some civil society organisations concurred that company profits would rise as a result of a transferable voucher and thus create an incentive to develop products to address the issue of AMR. However, they recognised that if this is done the system should be fine-tuned to meet the needs of patients. Others oppose this incentive as it would delay the entry of generics for other medicines and could increase substantially the costs for public health systems. Alternative solutions such as small milestone rewards or longer regulator protection periods should be considered according to civil society organisations, public authorities, healthcare professionals and citizens. In the public consultation, innovator industry defended the benefits of transferable vouchers. Public authorities, civil society and the generics industry expressed opposing views about the voucher citing arguments linked to overcompensation, high cost to health systems and loss of competitiveness for generics.

Impact of prudent use measures

The use of smaller packages would enable more sustainable use of antimicrobials and less release of unused antimicrobials in the environment. On the opposite side, it would increase manufacturing costs and package waste. Stricter rules on prescription of antimicrobials and mandatory use of diagnostics would impact prescription behaviour positively, however, it would also result in switching from broader spectrum antimicrobials to more specific (and expensive) antimicrobials and costly diagnostic tests. Requirements to adopt AMR lifecycle monitoring plans[152] would help the EU reduce its overall consumption of antimicrobials and hence AMR. This measure would come with some cost both to businesses and Member States, however the establishment of appropriate mechanisms to share information with regulators could mitigate this burden.

6.1.1.5 Horizontal measures[153]

The horizontal measures are intended to deliver wide-ranging improvements in terms of efficiency and effectiveness. **Table 11** presents a qualitative assessment of the benefits of each of the 10 pivotal horizontal measures, rating the likely benefits – against the baseline – on a 3-point scale (High, Medium, Low) for each stakeholder group. From this perspective, the most promising horizontal measures – overall, for all stakeholder groups – are the proposals to improve the governance of the European medicines regulatory network, the development of an integrated, pan-EU data architecture for the regulatory system and an EU-wide, centrally coordinated process for early dialogue.

[150] Unserved patients refer to those patients that were not served due to the delayed entry of generics, i.e. the lost volume
[151] 201020_EUJAMRAI_policy-brief_WP7_appropriate-use-of-antibiotics-one-health-perspective.pdf (eu-jamrai.eu)
[152] Such AMR lifecycle monitoring plan could cover stewardship, risk mitigation measures to limit AMR, report resistance to the antimicrobial, educational material to inform more efficient use, monitoring and reporting on the use.
[153] Detailed analysis of the measures are in Annex 11.

Table 11 - Qualitative assessment of the benefits of pivotal horizontal measures for key stakeholders

	Business	EMA	NCAs	SMEs	Health Systems	Environ-ment
Streamlining and de-duplication						
#1 Streamlining of procedures	H	M	M	H	L	L
#2 More efficient RUP	H	L	H	L	M	L
#3 Efficient governance of the European Medicines Regulatory Network	H	H	H	H	M	L
#4 Facilitate more efficient interaction across regulatory frameworks	M	H	M	M	M	L
Digitisation						
#5 Legal basis to allow network to analyse real world evidence	M	M	H	H	H	M
#6 Legal basis for setting up electronic product information for medicines	L	M	M	L	M	L
#7 Electronic submission of applications	H	H	M	H	L	L
Enhanced support and regulatory flexibility						
#8 Optimise regulatory support to SMEs and non-commercial organisations	L	M	L	H	H	L
#9 Adaptation of the regulatory system to support the use of new concepts	H	M	M	H	M	L
#10 EU-wide centrally coordinated process for early dialogue	H	M	H	H	M	L

Stakeholders' views are more convergent vis-a-vis horizontal measures. Reducing regulatory burden (e.g. through efficient governance of EMA committees and authorisation procedures, elimination of the renewal procedure and digitisation) can be considered as common ground both for industry and public authorities and improve the competitiveness of the EU as a global destination for businesses.

The introduction of electronic product information is supported by all stakeholder groups. For healthcare professionals and patients it is important to keep paper package leaflets in certain cases to ensure access to information for all patients. Member States want that the different national levels of 'digital readiness' are respected. The electronic product information will complement the current paper package leaflet of authorised, statutory information for each medicine, though in certain cases Member States could allow electronic product information only. It could have positive effects on shortages and will be more appropriate to the EU's multi-lingual environment. The electronic product information will have a limited, positive environmental impact from reducing the number of paper package leaflets and streamlining the logistics chain.

An EU-wide centrally coordinated process for early dialogue among authorities responsible for clinical trials, marketing authorisation, health technology assessment, and pricing and reimbursement will improve business predictability for companies (including SMEs). Such early dialogues are expected to provide guidance to companies on evidence generation along the medicine lifecycle. Clearer and more coherent evidence requirements will reduce uncertainty and investment risks for developers of innovative medicines, in particular in areas of unmet medical need (where developers often already face significant challenges due to the complexity of the diseases concerned). Early dialogues can therefore contribute to guiding and steering the investment and clinical development decisions of companies towards innovations with high added value for health systems and patients. They will also ultimately contribute to timely patient access to innovative medicines by providing clarity on evidence requirements of downstream actors for timely generation of appropriate evidence, facilitating and speeding up their decision-making.

Overall, these measures are expected to generate net benefit of up to €100m a year, shared among businesses and authorities (Annex 3) in the best case scenario.

6.1.2 Option A – combined impact of the measures

Conduct of business: Retention of the current period of RP for all new medicines and special incentives for UMN, comparative trials and EU-wide product launch would have a positive effect on businesses that can benefit from the incentives. However, this would negatively impact the generic and biosimilar industry as it would further delay their access to the market. Measures on security of supply retain the current requirements hence they would bring no additional burden.

Public authorities: Incentives providing longer data protection periods in general (whether to promote innovation or EU-wide market launch) would carry a significant cost to national health systems and payers by delaying generic entry. There would also be additional administrative burden for the EMA and NCAs involved in the assessment of the additional applications, UMN criteria and verification of product market launch information to determine whether a MAH has fulfilled all the conditions to be eligible for longer data protection. On the other hand, a special incentive for comparative trials would offset an additional period of high prices for payers against a more robust evidence base for HTAs and payers.

The high cost of a transferable voucher given to developers of novel antimicrobials would be borne by healthcare payers. This cost needs to be considered in the context of the health costs related to AMR and possible savings from novel antimicrobials to combat resistant bacteria.

Sectoral competitiveness, trade and investment flows: The special incentives for UMN, including the transferable voucher and EU-wide market launch are expected to improve competitiveness and attractiveness of the EU pharmaceutical sector, especially SMEs and support increased investment in medicine development to address UMN and AMR respectively.

Research and innovation: The special incentives will support increased return on investment for developers and bring additional investment into R&D for UMN, including AMR. Comparative trials will contribute to better understanding the clinical benefits of a medicine and its comparators.

Functioning of the internal market: The slight increase in the number of new innovative centrally authorised medicines owing to incentives and the increase in access to those medicines through the market launch incentive will improve the functioning of the internal market. On the other hand, delayed generic entry would hinder competition, and keep prices high for a longer period compared to the baseline. Overall, option A would make more harm to the functioning of the internal market than benefit.

Administrative burden on business: Changes to RP for medicines to make them contingent on market launch should be expected to make the system considerably more complex. It will require reporting by MAHs on market launches resulting in higher administration costs. The horizontal measures however would significantly cut red tape.

SMEs: The transferable exclusivity voucher is intended to reward antibiotic developers that are often SMEs. Thanks to the transferability, they can monetise the value of the voucher by selling it. Fulfilling the conditions for the market launch incentive is more challenging for SMEs compared to big companies that may have offices and staff in all Member States. As mentioned in the 'SME test' Appendix D of Annex 12, other measures in Option A present no major positive or negative impacts.

6.1.3 Option B – combined impact of the measures

Conduct of business**:** For originators affected by the reduced RP, the overall income and profitability from new medicines would be significantly reduced (22% loss in commercial value). It may happen that developers increase their prices or otherwise rebalance their portfolios towards those market segments with greater commercial potential. The threat to EU-based originators will be offset to some degree by giving a boost to EU's generic industries, broadening their portfolios and potentially creating a prime-mover advantage in global markets. Similarly, developers of products addressing UMN will be exempt from the negative impacts of the measure.

A pay or play model would impose additional costs on EU pharmaceutical businesses, and while a minority may look to avoid a levy by developing antimicrobials or acquire businesses with an antimicrobial in their portfolio, the majority would be likely to view the surcharge as an unavoidable additional cost to be factored into their wider pricing policies.

Public authorities: Health payers may benefit from lower average lifetime costs for medicines due to earlier generic entry (because of a reduced data protection period). The extent of these benefits will depend on originators' response to the reduced incentives, and it is possible that average prices will be adjusted upwards to some degree to offset the shortened protection period.

Greater transparency around public support for medicines development may strengthen payers' position when negotiating with MAHs, helping to place a downward pressure on prices and thereby helping to maintain or improve access to medicines. Auditing the claim of developers demonstrating the absence of return on investment can be time consuming for authorities; the global development and the complex accounting systems raise questions on the overall feasibility of the exercise.

The measures to increase patient access to medicines are expected to improve the situation in particular in smaller markets, and thus the cost-effectiveness of the health systems.

Creating the infrastructure and monitoring shortages will require a significant investment from authorities. However, shortages avoided reduce the burden of finding substitutes or new suppliers.

Sectoral competitiveness, trade and investment flows: Reduction in the standard regulatory protection could weaken the global competitiveness of EU based originators overall, compared with the current situation. The reduction will affect equally all companies selling their products in the EU, no matter where their R&D is placed. The proposed pay or play model and access obligation would raise the cost of doing business in EU. This could affect the competitiveness of pharmaceutical companies in EU relative to non-EU companies.

Research and innovation: The reduction of the regulatory protection would cause an estimated annual €670m loss for R&D.

Functioning of the internal market: Earlier generic entry due to lowering of the standard data protection period for most new medicines (except those addressing an UMN) and increase in access to medicines through market launch obligations improve access to medicines and the functioning of the internal market. Reduced number of new innovative medicines would offset parts of the benefit.

Administrative burden on business: For developers that need to demonstrate the absence of a return on investment (ROI) from their R&D to secure a period of additional regulatory protection, there would be increased administrative costs associated with the methodology that businesses would need to follow. The transparency requirements would put an additional burden on companies. The horizontal measures however (discussed in section 8) would significantly cut red tape.

Obligations on MAHs to place centrally authorised medicines on the market in a majority of Member States may carry additional costs to the MAH that would have to bear the consequences of the reduced regulatory protection. The MAH will also have to provide additional information to regulators to demonstrate their compliance with obligations, raising costs. These obligations will also increase the costs to MAHs for interacting with HTA bodies in the Member States.

Administrative costs would also be expected for AMR measures in relation to the pay or play model and prudent use measure, e.g. monitoring of consumption.

SMEs: SME originators may find it more difficult to invest in riskier novel medicines given the reduction in future returns on investment owing to reduction in the standard data protection period and their relatively weaker market position when it comes to negotiating prices. On the other hand SMEs could benefit from the UMN incentive as they are often willing to invest in more risky R&D.

Obligations for market launch in a minimum number of Member States, including smaller markets, may be more challenging to meet for SMEs that do not yet have market presence.

6.1.4 Option C – combined impact of the measures

Conduct of business: Under this option, companies will be able to obtain the same protection period as in the baseline, but subject to compliance with certain conditions on which the eligibility for those "conditional" periods depend. Access to additional incentives for market launch and supply in all Member States, innovation for UMN and AMR as well as comparative trials will grant MAHs a longer period of exclusive prices compared to the minimum period being introduced, representing increased revenue and potentially changing behaviour of the sector. For companies not complying with the criteria for the conditional periods, impacts to conduct of business will be similar to those for Option B with reduction in overall income and profitability for new medicines. In addition, generic companies have the opportunity to enter the market earlier when originators have not fulfilled the RP prolongation conditions.

As regards shortages, submission of shortage prevention plans and additional reporting requirements to increase transparency of the supply chain would be acceptable to industry stakeholders if the information remains confidential, as this could be commercially sensitive. In consultations, industry stakeholders have strongly opposed applying these measures to all authorised medicines rather than limiting it to critical medicines and those medicines at high risk of shortage.

Public authorities: It is a win-win for public authorities, partly because their role in market launch is strengthened and no longer depending on companies only. Either after a successful price or reimbursement negotiation the medicine will become available to patients, or if there is no compliance, the measure will allow earlier market entry of generics and biosimilars thus reducing prices through generic and biosimilar competition. The strengthened role of Member States comes though with increased responsibilities for timely decisions at national level. The special incentive for comparative trials would lead to increased availability of such data to regulators at time of authorisation and may provide a better evidence base for HTAs and payers.

There may be additional costs for the public authorities involved in the assessment of UMN criteria and verification of product market supply to determine whether a MAH is eligible for longer data protection. Similarly, an increase in notification period for withdrawals and shortages will increase the complexity and administrative burden of monitoring shortages for Member States' authorities, although use of a common template and streamlined reporting for reporting could enable cost savings in the long term. Monitoring of supply at Member State level is economically advantageous for NCAs as it builds upon the existing system of national monitoring.

To support market launch of products in Member States, HTA, pricing and reimbursement bodies would have to conduct a greater number of procedures, in a reduced time period. It is observed that national pricing and reimbursement decisions for new medicines often take longer than the legally maximum of 180 days.[154] This can be partly offset by the efficiencies in the new HTA regulation, in particular better sharing of evidence on the therapeutic benefits of the treatment. Greater transparency around public support for clinical trials would strengthen pricing and reimbursement agencies' negotiating position with MAHs.

Member States would have new burden from supplying marketing authorisation holders with confirmations, refusals or waivers on the compliance with conditions for market launch extension. For AMR, public authorities would need extra capacity to assess AMR lifecycle monitoring plans.

The EMA and NCAs may require additional capacity and expertise or incur greater administrative burden in reviewing and assessing products based on the additional requirements for ERA and GMP (AMR aspects).

Sectoral competitiveness, trade and investment flows: By providing additional incentives (UMN, AMR, comparative trial) companies could get the same regulatory protection period as in the

[154] The Directive 89/105/CEE sets a maximum period of 180 days. For compliance issues see e.g. SWD(2012) 29 final.

baseline (8+2), and the EU pharmaceutical sector would remain attractive. In recent years, global venture capital investment has seen accelerating growth driven by advances in drug research and residual unmet need for which it is often easier to demonstrate value to patients/the healthcare systems[155]. The conditional EU-wide market launch incentive would apply to both EU and non-EU based companies, therefore the relative competitiveness of EU companies would not be driven down. The greater obligations and requirements to monitor and prevent shortages (including reporting and stockpiling requirements) and to address environmental challenges could affect more the EU pharmaceutical sector, but these measures are proportionate to achieving the objectives of security of supply of medicines at all times and reducing the environmental impact of pharmaceuticals. The overall balance of the measures on competitiveness would still be positive.

Research and innovation: Impacts on research and innovation would be similar to Option A.

Functioning of the internal market: The increase in the number of new innovative medicines owing to incentives and the increase in access across the EU through the market launch incentive will improve patient coverage and functioning of the internal market. Transferable vouchers would delay the start date of competition for the product to which the voucher is transferred, but the systemic impact would be limited due to the low number of vouchers and products benefiting from them.

Administrative burden on business: Additional regulatory data protection period for medicines contingent on appropriate and continuous supply will require MAHs to seek confirmation of supply from Member States resulting in higher administration costs. Similarly, an increase in notification period for withdrawals (12 months) and shortages (6 months) will increase the administrative burden of reporting shortages for MAHs. Introduction of a common template for reporting withdrawals and shortages could help reduce the additional administrative burden and promote harmonised data collection. Keeping monitoring at Member State level will not lead to additional burden for MAHs as it builds upon existing systems. MAHs will also incur greater costs due to requirements for stockpiling and shortage prevention and mitigation plans for all medicines. The horizontal measures however (see section 8) would significantly cut red tape.

Increased transparency around public support for clinical trials is narrower than the proposal under Option B, where all aspects of public support for medicines development, including various tax reliefs, have to be considered. Hence, this option would be simpler to implement as information on support of specific clinical trials through publicly funded R&D grants is more easy to retrieve and thus will incur less substantial administrative costs.

For AMR, prudent use measures would increase the administrative burden for businesses, e.g. for AMR lifecycle monitoring plans. Strengthened ERA would also increase the administrative burden for businesses.

SMEs: There may be additional administrative burden on SMEs to meet the strengthened requirements for ERA. The greatly expanded obligations and requirements for withdrawal/shortage reporting and management would also put a relatively larger burden on SMEs compared to their larger counterparts. On the other hand, SMEs should benefit from the introduction of regulatory sandboxes to support development of innovative products and scientific support from the Agency, as well as fee reductions. Incentives for UMN and AMR are also expected to benefit more SMEs, including biopharmaceutical companies, as they are more active in risky early-stage drug discovery.

6.2 Social impacts

Public health and safety is the key impact assessed under the social dimension of the legislation and includes patients' and health system interests.

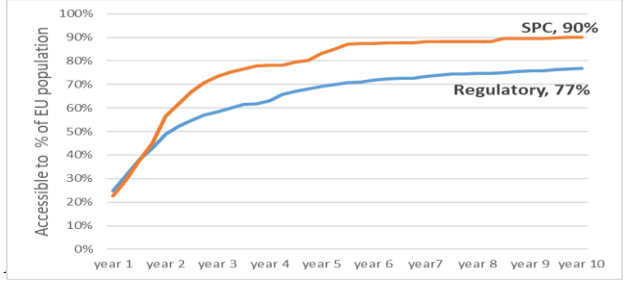


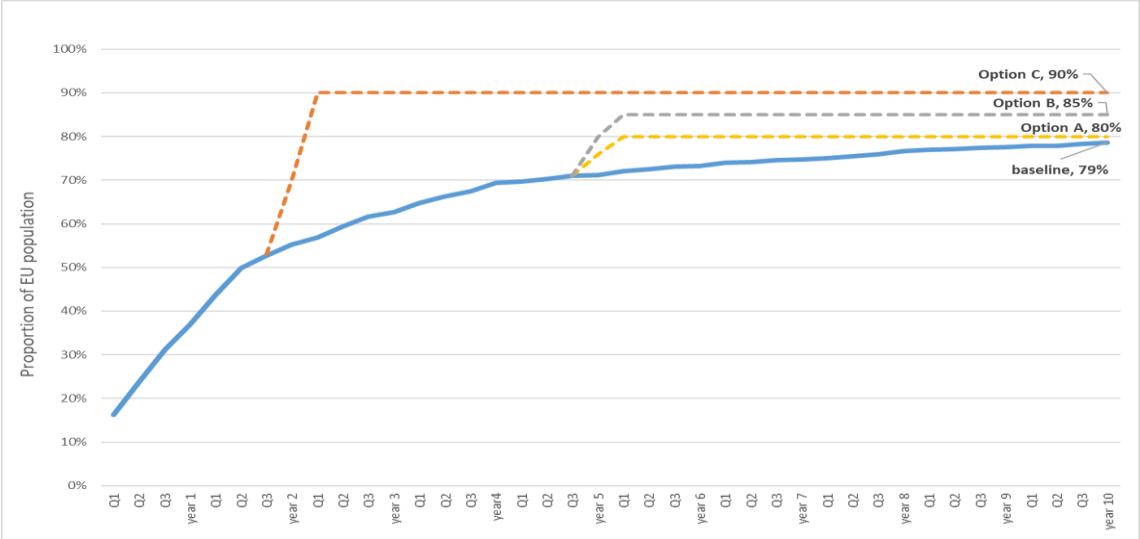
Figure 8 Avg product accessibility to EU population

[155] The financial ecosystem of pharmaceutical R&D: https://www.rijksoverheid.nl/documenten/rapporten/2022/02/28/tl

Among the specific objectives of this revision, the one on **access** is directly impacting patients. Analysis of historical data[156] reveals that access to newly authorised medicines in the EU is unequal and there is a large variation in time to access. Moreover, medicines whose last layer of protection is SPC are more accessible than RP protected ones (**Figure 8**).

All policy options seek to address this objective, using either incentives or reducing protection in case of non-compliance. **Figure 9** shows the likely social impact of the various options. We compared the options to the baseline in terms of time to access and proportion of EU population gaining access to a model RP protected medicine.

Figure 9 Proportion of EU population gaining access over time in various options



Based on the assumed compliance rate (Option A – 50%, Option B – 75%[157], Option C - 66%) and time limits to comply, we modelled when and what percentage of the EU population can gain access to the average RP protected medicine (see also section 6.1.1.3).

Option C outperforms all options, by providing access on average to 80% of EU population over the 10 years protected period, 15% higher than in the baseline (65.3%). Also options A and B offer a higher access than the baseline (67.6% and 70.2% respectively). In other words, in Option A 11 million, in Option B 22 million and in Option C 67 million more EU citizens would have access to a typical RP protected medicinal product, should they need it[158] compared to the baseline.

The special incentives under Options A and C should support increased R&D investment, especially in areas of UMN and this should flow through to an increase in treatment options and benefit more patients. Comparative trials will provide a better evidence base for reimbursement decisions, potentially leading to cost-effective medicines becoming more readily available to those that need them. Such trials also tend to assess patient relevant parameters, such as their quality of life and provide better information to healthcare providers for evidence based treatment decisions.

The reduced regulatory protection in Option B would allow earlier generic/biosimilar entry, lower prices and eventually increase the number of patients treated with the concerned medicines. The positive impacts would be somewhat offset by reduced innovation, and the delayed or no entry of some innovative products to the EU market.

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[156] See Annex 4 (analytical methods and methodology) and Annex 5 (evaluation SWD).
[157] Not all, but for majority of markets.
[158] The medicines that were modelled with the average medicine, can be manifold in fact. They may address a small or big patient population, can offer higher or lower therapeutic value, therefore we refrained from converting the coverage rate into QALYs or other similar indicator that could thus compromise the integrity of the analysis.

The transferable exclusivity voucher in Option A and C would help develop novel antibiotics. While the scheme would apply to a limited number of novel antibiotics which need to be used selectively, i.e. as a last-line therapeutic option (to avoid bacteria developing resistance against them), they serve as an 'insurance' scheme for the EU and global population. The growing threat of antimicrobial resistance means that routine hospital procedures such as a hip replacement or a caesarean section can turn fatal. So far, these events are sporadic within the EU, but can develop into a dangerous public health emergency in the future. Novel antibiotics on the shelf can protect citizens from such a crisis and the health and economic cost of AMR in case of inaction may be much higher. Moreover, strict conditions for defining a 'novel' antibiotics will help to ensure that this incentive is not just a windfall profit for products already in the (weak) pipeline, but encourage additional investment in research.

In the public consultation, stakeholders rate access to medicines in the EU as ‘moderate’ or ‘poor’ (64.1%). The favoured policy responses differ between respondents; industry placing the root causes as factors outside the control of the legislation, and public authorities and patients advocating for obligations or conditions as incentives for access or stronger notification requirements (e.g. for shortages and withdrawals). For AMR, the highest ranking measure to address AMR was introduction of a ‘pay or play’ model (Option B) mostly supported by civil society organisations and opposed by the industry which supported additional market protection period for novel antimicrobials and the transferable exclusivity voucher.

6.3 Environmental impact

To address the issue of pharmaceutical residues in the environment, and in drinking and natural waters, different measures have been considered under the policy options. The general pharmaceutical legislation addresses the impact of pharmaceuticals in the environment through requirements for an environmental risk assessment (ERA) and related conditions of use and mitigation measures along the lifecycle of medicines. These measures complement those under the environmental policy and legislation to reduce the environmental impact of medicines; several specific environmental legal acts are under review, see section 1.1.

A common measure across all policy options is the more prudent prescription rules for antimicrobials, which should result in fewer antibiotics entering the environment.

For Option A, the current **ERA requirements** continue with an additional obligation to include the information on the environmental impact of the supply chain in the application dossier. The impact of Option A would not be very different to the baseline, though a greater environmental awareness of the supply chain actors could be envisaged.

Option B increases the requirements for ERA, by including the assessment of the environmental risk of manufacturing as part of the marketing authorisation process. Option C would in addition strengthen the conditions of use of medicines and include AMR aspects in GMP to allow a more holistic assessment of environmental risk along the pharmaceutical lifecycle.[159]

The overall impact of options B and C should be less residues (e.g. genotoxic substances, antimicrobials) in the environment and less disruptions to the ecosystem and human health. Strengthening the ERA in the general pharmaceutical legislation is expected to have a positive effect by increasing environmental awareness and responsibilities in the pharmaceutical sector. Furthermore, a strengthened ERA will also provide an improved basis for taking environmental risk minimisation measures, enhanced obligations for ERA updates, monitoring of medicines use and conditions for prudent use. Enforcement should be strengthened as well. The inclusion of assessment of environmental risk of manufacturing in the ERA would allow tracking the environmental risks of manufacturing across the supply chain providing a more comprehensive assessment of the potential

[159] Annex 11 describes the assessment of the proposed measures (tables 47 and 64) in qualitative terms.

environmental impact of a new medicine, but the measure could result in high costs and administrative burden and pharmaceutical inspectors may not have expertise to check compliance.

For option C, inclusion of AMR aspects into GMP would help minimise amounts of antibiotics entering the environment via manufacturing and thus prevent or reduce emergence of AMR from manufacturing of medicines. Companies would have additional costs to comply with AMR requirements in GMP and public authorities would have additional enforcement costs.

Some limited positive environmental impacts are expected from digitalisation such as electronic package leaflet and electronic submission of applications in terms of reduced use of paper and streamlining of the logistics chain.

In the consultations, stakeholders have pointed out that the introduction of new rules at an EU level has been known to be a trigger for other regions, leveraging on EU actions. There is variable stakeholder support on strengthening the ERA which ranges from support for it to cover all stages of pharmaceutical lifecycle, from raw materials to end-product (public authorities and citizens) to views considering existing measures (controls, benchmarking on the manufacturing and disposal of products in the environment) stringent enough (industry). According to the targeted survey (Annex 2), the inclusion of assessment of environmental risk of manufacturing in the ERA was mostly negatively rated by industry while all other stakeholder groups viewed this option as bringing a positive impact. A workshop conducted for this IA confirmed the general view that there is a tension between reducing regulatory burden while expanding environmental obligations.

The policy options are aligned with the EU climate-neutrality objective and consistent with ensuring progress on adaption to climate change. The policy options aim at reducing medicine residues in the environment and thereby reducing the environmental footprint.

7 HOW DO THE OPTIONS COMPARE?

This section compares the expected impacts of the options in relation to the baseline in terms of their effectiveness, efficiency, coherence, EU-added value, proportionality and subsidiarity.

The comparison focusses on the pivotal elements as these have the most significant impacts and will allow clear differentiation between the options. The horizontal measures together with the pivotal elements respond to the objective of **innovation and** will impact on the objective of reducing regulatory burden and providing a flexible regulatory framework. The other objectives are mainly impacted by the pivotal elements alone. The overall comparison of the options against the relevant criteria is presented in **Table 12**. The complete analysis of all the elements is provided in Annex 11.

Table 12 Overall comparison of policy options

Criteria	Baseline	Policy Option A	Policy Option B	Policy Option C
Effectiveness: contributing to achieving the policy objectives				
Promote innovation,	0	++	-	+
in particular for unmet medical needs	0	+++	0	+++
Create a balanced system for pharmaceuticals in the EU that promotes affordability for health systems while rewarding innovation	0	--	++	+
Ensure access to innovative and established medicines for patients with special attention to enhancing security of supply across the EU	0	+	++	+++
Reduce environmental impact of the pharmaceutical product lifecycle	0	+	++	+++
Reduce regulatory burden and provide a flexible regulatory framework	0	+++	++	++
Effectiveness: other impacts				
Competitiveness, SME, single markets	0	+	+	++
Social impacts (patients, public health and safety)	0	++	+	+++
Environmental impacts	0	+	++	+++

Criteria	Baseline	Policy Option A	Policy Option B	Policy Option C
Efficiency				
Administrative and compliance costs	0	++	++	+
Savings and benefits	0	+	++	+++
Coherence	0	+	++	++
EU added value	0	++	++	+++
Proportionality and subsidiarity	0	+	+	++
Overall	**0**	**+**	**+**	**+++**

For efficiency, effectiveness, coherence and EU added value, the scores are given on the expected magnitude of impact as explained above: + + + being strongly positive, + + positive, + moderately positive, 0 neutral, – moderately negative, – – negative and – – strongly negative.

7.1 Effectiveness

Innovation

Option A offers the same default incentives for innovation as the baseline with some additional ones in particular for UMN and AMR. Overall, Option A is slightly more generous towards innovators, as in this option incentives can be freely cumulated. Option C on the other hand offers lower default incentives for innovation than Option A, however under Option C companies can still get the baseline protection period if they comply with certain conditions (market launch, UMN, comparative trials etc.). In Option C, the maximum period of RP is capped. Option B keeps the baseline protection period for UMN medicines, whereas for other RP protected originator medicines there will be a 15% loss in profits. We estimate that this translates into €670m loss to innovation funding annually. The pay or play model in Option B is considered less effective than the transferable exclusivity voucher of Option A and C in stimulating AMR related innovation. It is important to note that the revision does not affect the incentives pertaining to intellectual property rights (patents and SPCs). These offer IP protection to the invention(s) associated with the medicine and can extend the effective protection period beyond RP. As Figure 3 illustrates, for about half of the medicines on the market, SPC is the protection that expires last. This important incentive for innovation would still be available for most of the products on the market despite a modulation of regulatory incentives. The revised SPC regime will not change the duration, but streamlines the way an SPC can be obtained through a single granting mechanism or a unitary SPC and ensuring legal certainty for innovative companies.

Horizontal measures will facilitate the secondary use of health data, including real-world evidence, for innovators (including SMEs and academia), and for regulatory decision-making. Wider and more systematic access to real world evidence will be integrated in the lifecycle of a medicine, from early stage of development (complementarity with clinical trials data), to authorisation and post-marketing supervision. In this context, the European Health Data Space infrastructure will provide a significant positive economic impact of at least €5.4bn over the next 10 years, stemming from efficiency gains as a results of a less costly access to health data by reusers (€3.4bn), greater information transparency for policy-makers and regulators (€0.8bn), and increased value for patients, healthcare providers and innovators thanks to further reuse of health data[160]. The complementarity of this initiative with the European Health Data Space, via the facilitation of the secondary use of health data, will have a direct benefit for all pharmaceutical companies, including SMEs.

Option C combined with horizontal elements, especially simplification, regulatory flexibilities and digitalisation is more beneficial to innovation compared to the baseline.

[160] COM SWD(2022) 131 final https://data.consilium.europa.eu/doc/document/ST-8751-2022-ADD-3/en/pdf

Affordability

In terms of affordability, the general pharmaceutical legislation has a limited role to play, as pricing and reimbursement of medicines is a Member State prerogative. Nevertheless, the regulatory protection has an impact on affordability, as it delays generic competition and keeps prices higher. As demonstrated in section 6.1, two-thirds of the medicines are protected from generic competition thanks to their SPC or patent protection, therefore any change to the RP would have no effect on them. According to the draft impact assessment on the revision of the SPC legislation, the unitary SPC system would not significantly affect the entry of generics and biosimilars on less attractive (smaller or peripheral) markets in the EU; the larger and more central EU markets usually remain unaffected as SPCs are sought there anyway. This is possibly so as other factors play a far more important role in a decision to enter a market, such as: pricing and reimbursement rules, legal uncertainty connected to the country, quality and readiness of healthcare systems, differences in the value assessment process, overall levels of pharmaceutical spending and size of the market. The additional annual expenditure on medicines that might be a result of wider territorial SPC coverage due to the unitary SPC is estimated at €37m.[161]

With these limitations, Option B offers the most effective measure in terms of affordability, offering €1.13bn direct cost reduction for health payers with the reduced RP period (6+2 years). This reduction of 0.5%-0.6% of the EU pharmaceutical expenditure would heavily impact 20-25%[162] of the new medicines (they would lose 15% of their gross profits) while other, often more profitable, medicines would be unaffected. Option A keeps the baseline protection period. The R&D transparency requirements in option B and C are supposed to indirectly contribute to affordability too, better equipping with additional evidence national bodies for price negotiations.

The market launch in option B is an obligation with no additional period of protection whereas in option C market launch is linked to an incentive. In both cases, if the market launch does not take place, it would at least result in cost savings to the public as non-complying medicines would lose a part of their protection period resulting in an earlier entry of generics or biosimilars. In option A, the market launch incentive would come with an extra €455m cost to the public. Options A and C offer additional incentives for UMN, and for the transferable exclusivity voucher, which come with additional costs. This is a **trade-off between innovation and affordability.** Options A and C also offer an incentive for comparative trials, however the cost of that incentive is counterbalanced by savings to the health systems by more informed pricing and reimbursement decisions, with an expected overall neutral/positive impact on affordability. However, this could not be quantified.

Options B and C include an expansion of the so-called Bolar provision to facilitate market entry of generic and biosimilar medicines immediately after the expiry of regulatory or intellectual property right protection periods. Market entry of these medicines lower generally the price of the innovator product and are themselves cheaper[163] and thus make savings for the healthcare systems, e.g. in 2020, the list price savings (excluding confidential rebates and discounts) accounted for €5.7bn in savings from biosimilar medicine versus the pre-biosimilar cost of the originator[164].

Option C is the most advantageous by far from a patient/public health perspective, and it represents a fair balance between originator and generic industry, along with public authorities and payers.

[161] Based on historic data (2010-2021) the country with the most significant estimated impact was Latvia in 2019, where additional spending could reach up to 0.48% of pharmaceutical expenditure, cf. section 6.6.2 of the draft SPC IA.
[162] Those having SPC or patent protection, having an orphan market exclusivity, or having an UMN or no return on investment status in option B would be exempt from the impacts of the decreased RP.
[163] Analytical report, indicator AFF-6, Annex 10.
[164] The Impact of Biosimilar Competition in Europe, December 2021, IQVIA.

Access and shortages

All options result in more and quicker market access of new medicines, compared to the baseline. The least increase is with Option A and that is the costliest measure for the public. Options B and C are not only more effective, but they are synergistic with affordability. In these options, the public wins in either case: more timely access across the EU if companies comply with market launch conditions, or earlier generic competition and affordability if they do not. The gain in access is highest with option C, thanks to the shorter deadline to compliance (2 years) and to the all-EU launch requirement (vs majority of Member States in option B).

Option A does not represent a significant change to the baseline in terms of shortages management, whereas Option B proposes a more coordinated reporting system, and option C even goes beyond that, and also requires earlier notification in case of shortages and withdrawals. As such, Option C has the highest positive impact on shortages, followed by B and A. There is a trade-off among shortages and administrative burden, better and more reporting is needed to address shortages but that comes with a certain administrative cost.

Environment

Option A does not impose additional requirements for the ERA, whereas Option B obliges companies to report about the environmental risks of manufacturing too as part of their MA application. Option C goes further than B, demanding more stringent conditions of use for medicines than the baseline. As with the shortages, there is a trade-off among environment protecting measures and administrative burden.

Regarding the impact on AMR, Option C offers the highest safeguards against the impacts of the release of antimicrobials into the environment, followed by option B, and with no impact for option A. All options feature prudent antibiotic use measures, to reduce antibiotics in the environment, and lower the risk of AMR. Options A and C are also the most effective in financing Europe's 'fair share' of the cost for novel antimicrobial development through a transferable exclusivity voucher while in Option B the 'pay or play' model would not directly increase the number of novel antimicrobials and may risk increasing prices in a broad range of medicines without resulting necessarily in the development of novel antimicrobials (while for the voucher this would concern only the product on which the voucher would be applied).

Regulatory burden and providing a flexible regulatory framework

Horizontal measures feature uniformly across the options, and they will represent a very significant burden reduction for companies and public authorities, through streamlining of procedures, digitisation, enhanced support and regulatory flexibility. In terms of regulatory burden, the difference among the options is restricted to the increased requirements due to more stringent shortages and environmental measures, where options C and B score worse than option A. However, this difference compared to the positive impacts from the horizontal measures is minor.

Impacts on competitiveness and SMEs

In terms of effect on **competitiveness**, the proposed incentives do not make a geographic distinction, they equally offer regulatory protection for products developed in the EU, or anywhere in the world which ensures a level playing field between EU-based and third country-based companies. While the EU regulatory framework is attractive for developers, competitiveness also depends on many other factors e.g. tax system and incentives; available grants, loans and other funding (e.g. the European Innovation Council Accelerator); pool of talents; proximity of top academia; clinical trials infrastructures; market size; security of supply chains; favourable reimbursement decisions.

The horizontal measures described in section 5.2.5 (e.g. simplification, digitalisation, elimination of duplications) and those pertaining to innovation and the futureproofing of the legislation (e.g. flexibility of the framework, clarification of scope, sandboxes, codification of rolling reviews and PRIME) are applicable to all options. They are set to enhance the attractiveness of the EU framework globally. In this context, other policies and initiatives working in synergy with this

revision, like the R&I policy, industrial strategy, the EU system of intellectual property rights (patents and supplementary protection periods), the creation of the European Health Data Space, are key factors to promote innovation and EU competitiveness.

In terms of **effects on SMEs,** Option A emphasises support for innovation, but otherwise presents no major positive or negative impacts for SMEs specifically. Option B includes several measures that are expected to negatively impact SMEs disproportionately. In terms of innovation, SME originators may find it more difficult to invest in riskier novel medicines given the reduction in the standard data protection period and their relatively weaker market position when it comes to negotiating prices. In terms of obligations for market placement in a minimum number of MSs, including smaller markets, may be more challenging to meet for SMEs that do not yet have market presence or distribution channels in such markets. The proposed measures in Option C would be the same for big pharma and SMEs, however some of the measures may have greater impact on SMEs, e.g. due to their limited ability to absorb such a reduction in market protection. Mitigating measures such as longer timeframes to comply with requirements for market launch for example would eliminate any disproportionate burden on SMEs. Regulatory sandboxes and the transferable exclusivity voucher for novel antibiotics could be especially beneficial to SMEs because they are more active in innovative fields than big pharma. Similarly, incentives for UMN would benefit SMEs, which are generally willing to make early-stage investments in areas of high risk, by giving more value to their assets even if they are acquired by big pharma in late-stage development. SMEs already enjoy fee exemptions and reductions for regulatory procedures and through the new horizontal measures SMEs will benefit from optimised scientific support with a greater likelihood of success for authorisation. Overall, with the increasing investment in biopharmaceutical R&D and the increasing share of SMEs among developers, biopharma SMEs in the EU and elsewhere would have excellent prospects for the future.

Overall, Option C scores the highest in the multi-criteria analysis, this option addresses the most effectively the specific objectives of the revision, and has the most positive economic, social and environmental impacts.

7.2 Efficiency analysis

This section compares the cost-effectiveness of the policy measures in the different options, based on the models and calculations in section 6. The data in tables are always compared to the baseline. The measures tackling access and affordability (changes in the regulatory protection period) and the incentives for UNM and AMR are the ones expected to have the most substantive economic impacts on the various stakeholders. Tables 13a, 13b and 13c compare the options with all relevant measures (the cost-benefit analysis of the variation to option C is presented in section 8.1).

Table 13a Cost-benefit table of key measures in **Option A**

Option A	Cost/benefit for public payer and patients	Cost/benefit for originators	Cost/benefit for generic industry
+1 year extension of RP for medicines addressing **UMN**	+ €246m cost + 1-2 new UMN addressing medicines	+ €282 gross profit (3 incentives)	- €39m gross profit
+6 months extension of RP for conducting **comparative clinical trials**	+ €328m cost + faster access and cost saving thanks to improved reimbursement decisions	+ €378m gross profit +€280m cost (8 medicines)	- €52m gross profit
+6 months extension of RP for all EU **market launch**	+€455 m public cost +3% access	+€527 m gross profit (7 complying medicines)	- €71m gross profit
Transferable exclusivity voucher	+€441m cost + 1 novel antibiotic	+€387m gross profit (1 voucher)	- €54m gross profit
Total balance	**+ €1.470m cost** + 1-2 new UMN medicines +comparative data +3% access +1 novel antibiotic	**+€1.294m gross profit**	**- €216m gross profit**

Table 13b Cost-benefit table of key measures in **Option B**

Option B	Cost/benefit for public payer and patients	Cost/benefit for originators	Cost/benefit for generic industry
2 year **reduction of RP** (except for UMN)	+€1860m gain innovation loss	**-€1.970m gross profit** (9-12 medicines)	+€266m gross profit
Loss of RP, if no **market launch** in majority of EU within 5 years	+€681m gain +5% access	**-€842m gross profit** (4 non-complying medicines)	+€101m gross profit
Total balance	**+ €2.541m gain** +5% access innovation loss	**- €2.812m gross profit**	**+€367m gross profit**

Table 13c Cost-benefit table of key measures in **Option C**

Option C	Cost/benefit for public payer and patients	Cost/benefit for originators	Cost/benefit for generic industry
2 year conditional protection for **all EU launch in 2 years**	€444 m gain +15% access	-€469m gross profit (5 non-complying MP)	+€63m gross profit
+1 year extension of RP for medicines addressing **UMN**	+ €246m cost + 1-2 new UMN addressing medicines	+ €282m gross profit (3 incentives)	- €39m gross profit
+6 months extension of RP for conducting **comparative clinical trials**	+ €328m cost + faster access and cost saving thanks to improved reimbursement decisions	+ €378m gross profit +€280m cost (8 medicines)	- €52m gross profit
Transferable exclusivity voucher	+€441m cost + 1 novel antibiotic	+€387m gross profit (1 voucher)	- €54m gross profit
Total balance	**+ €571m cost** + 1-2 new UMN medicines +comparative clinical data +15% access +1 novel antibiotic	**+€298m gross profit**	**- €82m gross profit**

The tables provide an overview of the costs and benefits of the different options and on different stakeholder groups. Whenever it was possible, we presented the cost/benefits in a monetised form, however for certain social benefits putting a monetary value was either not possible or not appropriate. Therefore the societal benefits of new UMN addressing medicines, of improved access, of new innovative antibiotics and of comparative clinical data of new medicines are only mentioned in the table, without a monetary value.

In terms of efficiency, option A delivers quite well on all targets and creates the desired societal benefits, however at a significant cost for the public, missing the affordability target. Option B on the other hand is very cost-efficient for patients and public payers, offering altogether €2.5bn savings to the public, around 1% of the annual pharma expenditure. Option B does improve patient access and UMN medicines would receive a relatively higher support (though unchanged compared to baseline). The savings to the public would be borne mostly by the originator industry.

Option C distributes the cost of the additional societal benefits more evenly among the stakeholders, and also effectively delivers on all objectives. In terms of efficiency, option C offers the most cost-effective mix of policy measures. The variation to option C (presented in section 8.1) equally delivers on all objectives in a cost-efficient manner, with a slightly different distribution of cost to offer more gains for public payers and patients.

Horizontal and other measures

In Annex 3, the analysis concluded that the horizontal measures are – in the best case scenario – expected to generate up to around **€300m savings annually regardless of the selected option**, shared among businesses (one-third) and authorities (two-thirds). Additional administrative costs resulting from measures on shortages and environment would offset as a minimum 10% of these savings (min. €30m additional cost) for businesses; likewise for administrations.

Option C offers the most cost-effective solution to achieve the specific objectives, followed by Options B and A.

7.3 Coherence

Options B and C are consistent with the EU Strategic approach to pharmaceuticals in the environment and complementary to the ongoing revisions of the environmental legislation mentioned in section 1.1. All policy options are coherent with the EU Action Plan on Antimicrobial Resistance[165]**.** All three options contribute to SDG 3 ("health and well-being), SDG 9 ("innovation and infrastructure") and SDG 10 ("reduced inequalities") [166] (section 1).

The objective of patient access to affordable medicines is coherent with the objective of the HTA Regulation on timely patient access. Option C with its incentives for both EU-wide access and comparative clinical trials provides the best alignment followed by Option A.

Through the horizontal measures all options will ensure coherence with the sectorial legislations medicines for rare diseases and for children, EMA fees legislation and with EU legal frameworks on medical devices/in vitro diagnostic and on BTC through efficient interaction and synergies between these regulatory frameworks. In addition, options B and C will create more clarity on the interplay between these legal frameworks through the proposed changes in definitions and classification advice. More details available in Annex 6 with regard to medicines for rare diseased and children and in Annex 9 for BTC.

The access related measures in Option C such as the modulation of incentives or the additional obligations of supply will not only have a positive effect on access but also a systemic effect on public and private actors' behaviour, as explained in section 6. At the same time, the European Health Data Space will provide actors access to harmonised EU health data which unlocks possibilities and efficiencies along the pharmaceutical lifecycle in the development of medicines promoting innovation, in the monitoring of medicines for both regulators and marketing authorisation holders and in evidence generation for downstream decisions after marketing authorisation.

The revision of the general pharmaceutical legislation and the revision of the SPC regime with a unitary SPC are coherent in the objectives to promote innovation and reduce regulatory burden. However, the unitary SPC may have a small negative effect on affordability, as mentioned in section 7.1, and a hypothetical risk[167] of delaying generic or biosimilar entry in markets, where the originator has never been present which would have a negative effect on patient access. On the other hand, the predictability for generic/biosimilar companies will increase in the new SPC regime, through a central SPC database, effectively streamlining decision, less risk of litigation and, if litigation occurs, the avoidance of multiple litigation. Together with the measures undertaken under the pharmaceutical revision to support day 1 entry of generics and biosimilars this will facilitate patient access to those products.

HERA would support solutions from the public procurement side to the market failures in the area of antimicrobials. This unprecedented, combination of policy changes is a result of a combined set of actions in related areas (data, procurement, pharmaceuticals) that complement each other and should not be seen in isolation from each other. Together with the futureproofing and simplification elements of this revision they constitute a holistic response which can be expected to radically upgrade the EU's position globally as a place for medicine innovation.

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[165] A European One Health Action Plan against Antimicrobial Resistance (AMR) (June, 2017), available at: https://ec.europa.eu/health/system/files/2020-01/amr_2017_action-plan_0.pdf

[166] Sustainable development in the European Union, overview of progress towards the SDGs in an EU context, 2022 edition, Eurostat (2022)

[167] The risk is considered hypothetical because it is only in very limited cases that generic or biosimilar medicines enter a market where a SPC has not been requested or granted, i.e. a market where the originator has never been present.

7.4 Proportionality and subsidiarity

All three options are consistent with the EU's right to act under the Treaty of the Functioning of the EU (covering public health protection, the single market and the free movement of products within the EU). Moreover, all three options propose actions that will allow the objectives of the revision to be addressed to a greater extent than if Member States were acting alone.

The principle of proportionality is strongly reflected in the discussion of certain trade-offs to be made between the different objectives (section 4). To give an example, trade-offs are inherent between the objective of innovation and affordability often achieved by generic/biosimilar competition. The incentives will remain a key element for innovation but they have to be adapted to better take into account that medicines are not sufficiently accessible by patients in all Member States. This is reflected in Option C which modulates incentives to reward innovation, especially for UMN, but also make the regulatory protection period conditioned to market launch in all Member States. If this condition is not fulfilled generic competition will start earlier, resulting in increased affordability.

With regards to subsidiarity, all options pursue the objectives of the revision and provide a clear demarcation between EU level and Member State level actions. They do not propose any change to the national health care systems which are in the exclusive power of Member States (Article 168 TFEU), but certain measure (e.g. transparency requirements, better evidence base, early dialogue between regulators, HTA bodies and payers) will facilitate decisions of Member States in these areas e.g. pricing and reimbursement.

7.5 Limitations of the comparison

There is a level of potential uncertainty in the findings described in section 7 owing to the influence of other contextual factors such as developments in the pharmaceutical sector, other relevant legislations (e.g. HTA Regulation, Urban Waste Water Directive and SPC Regulation) and policies at Member State level (see for details of factors influencing access to affordable medicines – annex 14). While the influence of external factors has been considered in the design of the options and their analysis there is an unavoidable risk that they may impact or delay some of the expected benefits. Their effects and anticipated unintended consequences (e.g. the effect of some measures on prices of medicines, or the effect of conditionality of certain incentives on innovation) are analysed to the extent possible in section 6. There is also a level of uncertainty owing to the limitations and assumptions involved in assessing and quantifying the likely impacts of the options provided.

All methods applied to our research encountered a varying degree of difficulty in relation to lack of quantitative data available in the databases and sources examined. We did not find enough data to quantify all relevant impacts of every policy measure discussed in the policy options for the future of the legislation. Whenever possible, we have made reasonable assumptions to assess the impacts, but this lack of quantitative data is a key limitation to our analysis.

8 PREFERRED OPTION

The impact assessment indicates that policy option C is most effectively addressing all the objectives of the revision of the general pharmaceutical legislation in an efficient and consistent manner. The measures of option C address in a proportionate manner the underlying problem drives; a mapping of measures against problem drivers can be found in Annex 16.

This option proposes a modulated trade-off between incentivising innovation (for both unmet medical need and antimicrobial resistance) and improving access, R&D transparency, and security of supply of medicines as well as reducing the environmental impact of medicines. The costs and benefits of Option C for different stakeholder types are described below. The below section considers the pivotal measures but also **takes into account the other measures assessed in Annex 11**, along with the impacts of the horizontal measures.

The preferred option conforms to the principles of subsidiarity and proportionality. It respects the national competence on the organisation of the Member States' healthcare systems and provides clear demarcations between EU level and Member State level actions. Given the objectives the revision aims to achieve, the trade-offs and new burdens on companies and authorities are acceptable and proportionate.

It is expected that the revision will not change the current legal instruments, i.e. a Directive and a Regulation, for the general pharmaceutical legislation.

8.1 Costs and benefits of the preferred option

Table 14 reviews the most significant costs and benefits stemming from the pivotal measures, and also includes the variation to Option C described in section 5.2.4. The variation would decrease the 2 year conditional protection to 1 year. As a result, the overall protection level moves down by 1 year for all RP protected medicines, and only 1 year protection remains dependent on the launch condition. The 1 conditional year is a lower "prize" for compliance, thus we assumed that fewer medicines would meet the requirement (50% vs. 66% in the default). The variation allows the legislator to consider the impacts on the various stakeholder groups by "moving the cursor".

Table 14a Cost-benefit table of incentives in Option C (6+2+2) compared to baseline (8+2)

Option C	Cost/benefit for public payer and patients	Cost/benefit for originators	Cost/benefit for generic industry
2 year conditional protection for **all EU launch in 2 years**	€444 m gain +15% access	-€469m gross profit (5 non-complying MP)	+€63m gross profit
+1 year extension of RP for medicines addressing **UMN**	+ €246m cost + 1-2 new UMN addressing medicines	+ €282m gross profit (3 incentives)	- €39m gross profit
+6 months extension of RP for conducting **comparative clinical trials**	+ €328m cost + faster access and cost saving thanks to improved reimbursement decisions	+ €378m gross profit +€280m cost (8 medicines)	- €52m gross profit
Transferable exclusivity voucher	+€441m cost + 1 novel antibiotic	+€387m gross profit (1 voucher)	- €54m gross profit
Total balance	**+ €571m cost** + 1-2 new UMN medicines +comparative clinical data +15% access +1 novel antibiotic	**+€298m gross profit**	**- €82m gross profit**

Table 14b Cost-benefit table of incentives in Option C Variation (6+2+1) compared to baseline (8+2)

Variation to Option C	Cost/benefit for public payer and patients	Cost/benefit for originators	Cost/benefit for generic industry
1 year general reduction of the RP	+€1,008m	-€991m gross profit	+€133m gross profit
1 year conditional protection for **all EU launch in 2 years**	+€384 m gain +8% access	-€378m gross profit (8 non-complying MP)	+€51m gross profit
+1 year extension of RP for medicines addressing **UMN**	+ €246m cost + 1-2 new UMN addressing medicines	+ €282m gross profit (3 incentives)	- €39m gross profit
+6 months extension of RP for conducting **comparative clinical trials**	+ €328m cost + faster access and cost saving thanks to improved reimbursement decisions	+ €378m gross profit +€280m cost (8 medicines)	- €52m gross profit
Transferable exclusivity voucher	+€441m cost + 1 novel antibiotic	+€387m gross profit (1 voucher)	- €54m gross profit
Total balance	**+ €377m gain** + 1-2 new UMN medicines +comparative clinical data +8% access +1 novel antibiotic	**-€602m gross profit**	**+€39m gross profit**

In the default Option C, the higher market access is achieved without extra cost to the public, even some gains could be expected in case of non-complying medicines. The other incentives would mean an extra cost to the public and to generics, nonetheless it is expected that the indirect benefits from the medicines addressing UMN and faster and better reimbursement decisions, would offset

these costs. The originator companies would have additional costs and benefits from the incentives and the market launch conditionality, and overall they would see an increase in their sales.

In the variation of option C the public would gain significantly compared to the baseline in monetary terms and also enjoy the benefits of the measures. The gains would even allow financing the transferable voucher to support development of novel antimicrobials, without turning the public monetary balance into negative. In the variation, all the costs of the positive social impacts would be translated into reduced revenues for innovator companies, though a significant proportion of the costs would come from non-compliance (e.g. not launching in all EU markets, not carrying out comparative trials), which companies should avoid by complying.

In the variation the cost is put only on a subset of innovator companies, e.g. high-sales, SPC protected medicines would be unaffected. The shorter conditional period for market launch (1 instead of 2 years) means a smaller loss of revenue if companies do not launch in all EU markets, therefore a lower compliance rate (50%) is assumed, resulting in smaller positive effect on patient access. The loss to innovators may translate into slightly less innovation.

Option C and its variant are both cost-effective alternatives to reach all the objectives, the slight difference between the two being the different focus on more access or more affordability (+15% access and €571m more cost vs. +8% access and €377m gains) for the public payer and patients.

Patients, Citizens and Healthcare services

Option C will bring **benefits to patients and citizens** by facilitating the work of healthcare professionals, pharmacies, hospitals and strengthening health. The new measures to promote access across all Member States, by incentivising companies to launch their products on all EU markets, coupled with lower revenues for companies in case of non-compliance will be the first EU-level legislative measure to address the long-standing inequalities **and will increase patient access to innovative medicines**. Facilitating the entry of generics and biosimilars will increase affordability and consequently increase the number of patients treated. The additional incentive for addressing UMN will incentivise the development of more medicines with high public health benefit. Transferable vouchers would lead to development of novel antimicrobials, reduce EU deaths and health system costs due to AMR, and ensure a better preparedness against the increasing threat of resistant bacteria. **Security of supply** measures will improve continuous availability of both critical and non-critical medicines, which will significantly reduce shortages of medicines and benefit patients and healthcare services. Citizens will also benefit from measures taken to reduce the impact of pharmaceuticals on the environment and on public health via the environment through a strengthened environmental risk assessment of medicines along their lifecycle and imposition of appropriate measures to mitigate these risks.

Several other measures discussed in Annex 11 will corroborate the impacts of the pivotal measures: Option C would give a push to repurposing of medicines, as a cost-efficient way to expand therapeutic uses of medicines instead of a rather selective and even risky off-label use (C.1.2., C.1.3.)[168]. Along with the measures facilitating generic entry right after protection expiry (C.1.4., C.5.1., C.5.2., C.5.4., C.5.5.), these will further expand patients' access to medicines. Prudent use measures for **antimicrobials** will help decrease the risk of AMR (C.2.3, C.2.4, C.2.5).

A harmonised system for authorisation of medicines in the EU – through the general pharmaceutical legislation – offers clear EU-added value for public health to enable access to and innovation of medicines. In addition, EU-level action is the most efficient mechanism – in the scope of this revision – to address the concerns Member States have raised about unequal access and affordability, in particular for the centrally authorised medicines.

[168] The codes in brackets refer to the codes of the measures in Annex 11for easier identification

Future proofing measures of Option C will ensure patient safety in areas of rapid technological change, including personalised medicine. Currently, Directive 2001/83/EC covers all 'medicinal products' that are "either prepared industrially or that are manufactured by a method involving an industrial process". "Delinking" the legislation's scope from the way medicines are manufactured will address potential regulatory gaps (without changing the overall scope) due to scientific and technological developments e.g. low-volume products, bedside-manufactured or single batch personalised medicines that do not involve an industrial manufacturing process[169] (C.3.3.). Adapted regulatory pathways, e.g. for less complex cell-based medicinal products, and regulatory sandboxes will also increase the chance of faster patient access to cutting edge medicinal products (C.3.5., C.3.6.). Lastly, allowing electronic product information will bring advances to readability for patients and opportunities for healthcare professionals to communicate information more effectively (Horizontal 6).

Industry

For the originator industry, the modulation of the regulatory protection means a lower standard **duration of regulatory protection**, but companies can achieve a similar/same (depending on the variant in this option) protection as of today if they comply with the **condition to launch in all EU-markets.** The extra condition would entail some additional administrative cost, but that would be somewhat compensated by burden reduction, such as allowing multi-country packs for certain types of medicines (C.4.2.). The special incentive for addressing UMN would offer a longer period of protected sales and thus a higher return on investment, a €282m additional gross profit at industry level. The special incentive for comparative trials will recompense the additional costs from carrying out the trials, and the data will help faster pricing and reimbursement decisions, and earlier market entry. It comes with €378m extra gross profit, but also with €280m cost. The trial data would allow better negotiating position for payers, which may limit company's profits. The transferable exclusivity voucher would reward developers of novel antibiotics, and also the buyers of the vouchers would have gains.

The incentives involving extension of data protection would delay generic entry and keep generic companies out of the market for longer. In the case of UMN incentive of an additional 1 year to originators, it represents a loss of €39m in gross profit per year for generic companies, and €52m for comparative trials. They would also have increased costs from the obligation to include smaller markets in their own mutual recognition procedure (or decentralised procedure) applications (C.1.5, C.1.6.). On the other hand, there should be an increase in R&D activity for generic/biosimilar medicines with a streamlined and clearer regulatory pathway (C.5.1.) and by measures facilitating generic entry right after protection expiry.

Option C also brings greater certainty for businesses by adding clarity and predictability to the regulatory system and the legal pathway (see references to "delinking" in the previous section, as well as adaptation of definitions), streamline the GMO assessment in the authorisation of clinical trials that involve investigational medicines with a GMO component (C.3.2.). These measures should promote **innovation** and attract investment to the EU. SMEs should also benefit from the introduction of regulatory sandboxes to support development of innovative products (C.3.6.) and enhanced support in addition to the current fee reductions.

The preferred option continues to provide a favourable incentive structure for innovation in the EU which remains competitive against what other regions offer. The incentives apply equally to all products, regardless of where they are developed – in the EU or elsewhere; in this regard, the EU competitiveness is not negatively impacted by this option.

[169] Organised in close coordination with other EU legal frameworks (medical devices, substances of human origin) to avoid shifts of therapies that are already regulated

Greater use of multi-country packs is also expected to facilitate the movement of medicines within the EU internal market, which will help all businesses. In terms of **security of supply**, option C introduces several obligations and requirements on MAHs and wholesalers that likely will carry additional costs to these parties including costs associated with warehousing (for stockpiling), operations and capital (C.6.1. to C.6.9.). Stakeholder consultations estimated that increasing warehouse capacity to accommodate 10% additional stock will have a cost of €500k – 1m per warehouse. This policy option will also require more **transparency** and at the same time obligations regarding supply chain actors and environmental risk assessments, which will result in additional costs for businesses for inspections, compliance and other additional responsibilities. This will likely represent a substantial burden on SMEs in particular.

The horizontal measures on the other hand simplify the regulatory system and reduce burden on industry, reducing compliance costs and administrative burden in the range of €80-160m per year.

For industry, a harmonised and predictable medicines regulatory framework – through the general pharmaceutical legislation – offers clear EU-added value by reducing duplication, simplifying requirements and making the system easier to navigate. The preferred option aims at harmonising requirement concerning shortages.

Despite the new obligations for companies, the preferred option is proportionate when balanced with the efficiency gains, including those from secondary use of health data via the European Health Data Space (see section 7.1), and simplifications introduced and the recognition that other objectives such as patient access and the wider policy ambitions on strategic autonomy and green deal have to be factored in.

Competitiveness and future of innovation under reduced regulatory data protection

Industry stakeholders frequently claim that the reduction of regulatory data protection period would harm future innovation and EU competitiveness. In section 6.1.1.2 we demonstrated that the incentives are agnostic to the geographic origin of the medicines, therefore the reduction would not harm EU companies more than non-EU companies coming to the European market (non-EU companies develop 80% of new medicines introduced to the EU market).

However, lower profits may transform into less innovation at a global scale. Option C results in a slight gain in gross profits but the variation of option C estimates a total loss of €602m in gross profits. Industry re-invests on average 25% of their gross profit into R&D, consequently €150m may be lost for innovation. In 2021 the global pharmaceutical industry has invested €230b in R&D[170], hence the potential loss amounts to 0.07% of global R&D investment. If we wanted to translate this to medicines, only 1 in the next 1500 new medicines would not be developed because of the reduction, a likely invisible loss over the next 15 years.

Public authorities, agencies and payers

Incentives involving additional data protection periods will lengthen the period in which health systems can be charged higher prices for medicines. For example, transferable vouchers would have indirect healthcare costs for the healthcare payer.

Public authorities will require additional budget and expertise for reviewing MA applications (larger number of applications, change in ERA requirements, etc.), enforcement of obligations (e.g. for market launch, lifecycle management of antimicrobials), inspections of manufacturing sites, increased commitments to provide advice (e.g. on interchangeability of biosimilar medicines, ERA, green manufacturing, classification of borderline products etc.) as well as setting up of new centralised infrastructure for information exchange (e.g. for shortage monitoring; one-off costs). Additional costs for EMA in assessing the application for new antimicrobials and the associated

[170] $238b - EvaluatePharma - World Preview 2022, Outlook to 2028, page 20

voucher are estimated at €2m per year. The workload of pricing and reimbursement agencies would also increase with incentives for market launch driving up the number of applications, while their workload should decrease from better evidence provided from more comparative trials.

Health payers would also benefit from measures to promote post-authorisation studies and comparative trials, which would enable access to evidence that supports pricing and reimbursement decisions for HTA bodies. Rejecting immature marketing authorisation applications at time of validation would reduce workload of medicine regulators (C.9.1.) with estimated savings for the EMA and NCAs at 3% of annual costs.

Measures to improve security of supply will facilitate information exchange between Member State authorities and improve strategies to tackle shortages. Both aspects should reduce long-term costs to authorities. However, public authorities will also need to increase capacity to assess shortage prevention plans provided by MAHs, and, depending on the cost and risk-sharing agreements for reserve stock, authorities may also incur direct costs for storage. While measures to improve quality, manufacturing and environmental impact of pharmaceuticals will increase workload for EMA and NCAs, increased coordination, joint audits and data sharing could also result in efficiencies.

Academic/research institutions

Option C will bring benefits for clinical researchers and academics in the form of opportunities to be more involved in the development work and trials, as a binding system for scientific assessment of evidence for repurposing off-patent medicines will be established (C.1.2), and obligations will be simplified to facilitate non-commercial entities (e.g. academic) to become MAHs (C.1.2). This option also brings increased requirements of efficacy and safety for use of hospital exemption (e.g. trial data and good manufacturing practices capability), dedicated pathways for less-complex cell based medicinal products and a regulatory sandbox (C.3.5. and C.3.6.), which may impact the activities of academic researchers and research institutions under this exemption, but should support data collection, safe and efficacious use and ATMP development. Academics and research institutions will also benefit from streamlining 'horizontal' measures such as fee reduction and more scientific support to help non-commercial entities to bring innovative medicines to the market.

8.2 REFIT (simplification and improved efficiency)

The review aims at simplifying the regulatory framework and improving its effectiveness and efficiency thereby reducing the administrative costs borne by companies and administrations[171]. The horizontal measures are envisaged in that regard and most of them will act on the core elements of the authorisation and life-cycle procedures, which are at the centre of this legislation. These measures can be grouped as follows:

Streamlining and acceleration of processes and coordination of the network

The proposed abolishment of the sunset clause and renewal of MAs after five years would avoid unnecessary duplication and a burden on MAHs and regulators[172]. The envisaged reduction in the number of notifiable variations could potentially reduce the administrative costs incurred by MAHs and regulators. For generic applications, in order to avoid duplicative assessments of the same data for medicines containing the same active substance, to reduce administrative costs for both administrations and companies, worksharing procedures and a more efficient repeat use procedure are proposed.

[171] A quantification of these costs is presented in Annex 3.

[172] The latter not adding value regarding safety, given the availability of Periodic Safety Update Reports that accumulate safety data and any impacts on the known benefit-risk balance.

The revision will also look to streamline efficient interaction (early dialogue) between different regulatory authorities (EMA, NCAs, HTA, etc.) as well as synergies between different but related regulatory frameworks, e.g. interplay with BTC framework, medical devices (for certain types of products) and health technology assessments. This, together with a structural simplification of EMA (e.g. as regards the committees) should further reduce the administrative costs for both the administration and the business.

Digitalisation

The envisaged revision aims at an enhanced digitisation of different applications to EMA and NCAs, which should result, overall, in cost reductions. This would induce initial, one-off, costs for the administrations but should bring efficiencies and therefore cost reductions with time. Finally, the envisaged use of the electronic product information, i.e. the electronic leaflet as opposed to paper leaflets, should also, in the long term, adduce additional administrative cost reductions.

Adaptations to accommodate new concepts and support SMEs and non-commercial organisation

The revision foresees adaptations to accommodate new concepts and regulatory processes such as adaptive clinical trials, use of real world evidence, and new uses of health data within the regulatory framework. This should result in cost reductions for businesses and administrations. It also envisages optimising the regulatory support to SMEs and non-commercial organisations. This should in turn result in additional reductions of administrative costs for these parties.

8.3 Simplification and burden reduction for businesses, supporting the one in one out approach

This section evaluates the administrative costs induced by the implementation of the *preferred* option for businesses and citizens/patients, in comparison to the baseline. Moreover, all options include some administrative costs related to horizontal elements, which are also evaluated in comparison to the baseline[173].

As regards companies, there are a number of cost reductions resulting from the implementation of the *preferred* option. The reduction is done for reasons of good policy but also in part to create the financial headroom to introduce new legislative actions and procedures that will inevitably bring additional costs in pursuit of additional social benefits. As a case in point, the strengthening of the environmental risk assessment within the overall assessment process (e.g. in consideration of manufacturing and supply chain issues) will add costs, compared with the current situation, as will the inclusion of environmental issues within post-market authorisation monitoring and the measures on security of supply.

As regards companies, there are also costs reductions resulting from the implementation of horizontal measures which apply to all the options. The revision aims at simplifying the regulatory framework and improving its effectiveness and efficiency thereby reducing the administrative costs. Annex 3 presents the cost for the horizontal measures that relate most directly to streamlining of processes and coordination of network as well as digitisation measures. The table summarises the balance of costs and benefits, and suggests that the measures as proposed may deliver a reduction in compliance costs and administrative burden in the range of €524.5-1,050m for the industry[174].

More specifically:

- The proposed streamlining procedures, including enhanced support, will yield useful cost savings for European pharmaceutical businesses, with estimated cost savings falling in the range of €412.5-825m over the next 15-years.

[173] A quantification of these costs and savings is presented in Annex 3.
[174] Methodological details underpinning the calculations are described in Annex 4.

- The proposed digitalisation measures will provide relatively modest financial savings to industry, given the primary focus is on the integration of regulatory systems and platforms across the EU and support for the re-use of data. Electronic submission will however deliver industry cost savings. These are estimated at €112m-€225m over 15 years.

For citizens/patients, there are many improvements foreseen in all areas of importance[175] but there are no obligations and therefore costs induced by the legislation.

9 HOW WILL ACTUAL IMPACTS BE MONITORED AND EVALUATED?

Indicators for the preferred option, in relation to the core objectives, with suggested data sources and proposed frequency of data collection are presented in table 15. The Commission will review the indicators periodically.

Much of the data collected by EMA are already collected today and published in its annual reports; the new data collected by EMA would result in only a minor additional burden. The burden on the Member States to provide data on the number of shortages, variations and authorised antimicrobials would also be minor, and even further reduced by digitisation. The Commission has access to the IQVIA data and data from the other sources are already being collected.

The development of medicines is a long process and the completion of clinical development plans can take up to 10-15 years. Regulatory protection periods of the preferred option exert their effect up to 11 years after marketing authorisation. For certain measures concerning incentives for innovation, affordability and access, a meaningful evaluation of the revised legislation can take place only 15 years from its application. The Commission will monitor though the indicators and assess the need for an earlier revision.

Table 15 Proposed list of monitoring and evaluation indicators

Specific objective	Monitoring indicators	Data source/frequency
Promote innovation, in particular for UMN	• Number of authorised medicines with new active substance • Number of authorised medicines addressing UMN • Number of authorised antimicrobials • Number of authorised novel antibiotics/transferable vouchers granted • Number of incentives granted for comparative trials • Use of pre-marketing regulatory support (scientific advice, PRIME) • Number of sandboxes used	• EMA data/annual • EMA/annual • EMA and NCAs/annual • EMA/annual • EMA/annual • EMA/annual • EMA/annual
Create a balanced system for pharmaceuticals in the EU that promotes affordability for health systems while rewarding innovation	• Market share of generic and biosimilar medicines • Development of prices of medicines • Member States' pharmaceutical spending	• IQVIA data/biannual • Euripid database, IQVIA data, OECD data/biannual • Eurostat, OECD data/biannual
Ensure access to innovative and established medicines for patients, with special attention to enhancing the security of supply across the EU	• Time from authorisation to market launch • Number of Member States where basket of medicines (both innovative and established medicines) are launched • Number of market access incentives granted • Number of withdrawal of medicines reported </> 1 year in advance • Number of withdrawals for which, as a result of the	• IQVIA data/biannual • IQVIA data/biannual • EMA and NCAs/annual

[175] The legislation aims at improving the flow of cutting-edge treatments for conditions for which there are no effective treatments currently (UMN), reversing the decline in investment in antimicrobial research and encircling the issues driving AMR, incentivising access in all Member States, a broader repurposing, and the generic and biosimilar entry. A more robust ERA will support environmental goals. Measures on security of supply will improve access to medicines.

	notification, measures could be identified to mitigate, prevent or alleviate a critical impact on the health system or on patients of the withdrawal • Total number of shortages • Number of shortages reported </> 6 months in advance, specifying number of critical shortages • Number, root cause and duration of critical shortages and identification of measures that mitigated, prevented or alleviated impact on the shortage • Number of NCAs automatically sharing information with the EMA platform and number of NCAs manually submitting information with the EMA platform	• EMA and NCAs/annual • EMA and NCAs/annual • EMA and NCAs/annual • EMA and NCAs/annual • EMA
Reduce the environmental impact of the pharmaceutical product lifecycle	• Presence of medicines residues in the environment • Consumption of antimicrobials • GHG emissions of EU-based pharmaceutical manufacturers	• Information Platform for Chemical Monitoring that includes data on occurrence of pharmaceuticals in the environment • ECDC annual report on antimicrobial consumption • Eurostat/annually
Reduce the regulatory burden and provide a flexible regulatory framework	• Number of variations • Number of meeting of EMA scientific committees and their working parties • Number of early dialogues/ scientific advice including other public authorities than medicine authorities • Number of scientific advice given to SMEs and academia	• EMA, CMDh and NCAs/annually • EMA/annually • EMA/annually • EMA/annually

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PART 2/2

COMMISSION STAFF WORKING DOCUMENT

IMPACT ASSESSMENT REPORT

Accompanying the documents

Proposal for a Directive of the European Parliament and of the Council on the Union code relating to medicinal products for human use, and repealing Directive 2001/83/EC and Directive 2009/35/EC

Proposal for a Regulation of the European Parliament and of the Council laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, amending Regulation (EC) No 1394/2007 and Regulation (EU) No 536/2014 and repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006

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1 GLOSSARY

Term or acronym	*Meaning or definition*
Accessibility	A medicine becomes accessible to patients once it has been authorised, is being marketed, and can be reimbursed in a Member State.
Affordability	Relates to payments to be made by health systems/public payers and consequently to the sustainability of public funding of the healthcare sector raised through social security contributions or taxes (affordability at macro level).
AMR	Antimicrobial resistance.
ATMPs	Advanced therapy medicinal products (ATMPs) are medicines for human use that are based on genes, tissues or cells, as defined in Article 2 of Regulation (EC) No 1394/2007. See also: Advanced therapy medicinal products: Overview | European Medicines Agency (europa.eu)
Availability	A medicine becomes available once it has been authorised in a Member State or centrally in the EU.
Biological medicine	A medicine whose active substance is made by or derived from a living organism. Biological medicines contain active substances from a biological source, such as living cells or organisms (human, animals and microorganisms such as bacteria or yeast).
Biomarker	Biological molecule found in blood, other body fluids, or tissues that can be used to follow body processes and diseases in humans and animals.
Biosimilar	A biosimilar is a biological medicine that is highly similar to another biological medicine which has already been approved. Biosimilars are approved according to the same standards of pharmaceutical quality, safety and efficacy that apply to all biological medicines.
CAT	The Committee for Advanced Therapies is the European Medicines Agency's committee responsible for assessing quality, safety and efficacy of advanced therapy medicinal products (ATMPs) and following scientific developments in the field.
CAP	The centralised authorisation procedure is The European Union-wide procedure for the authorisation of medicines, where there is a single application, a single evaluation and a single authorisation granted by the European Commission valid throughout the

	European Union.
CBA	Cost-benefit assessment
CHMP	The Committee for Medicinal Products for Human Use is the Agency's committee responsible for human medicines.
Class waiver	Class waivers provide an exemption from the obligation to submit a paediatric investigation plan for a class of medicines, such as medicines for diseases that only affect adults.
Conditional marketing authorisation	Conditional marketing authorisation is the approval to market a medicine that addresses patients' unmet medical needs on the basis of data that is less comprehensive than that normally required. The available data must indicate that the medicine's benefits outweigh its risks and the applicant should be in a position to provide comprehensive clinical data in the future.
COMP	The Committee for Orphan Medicinal Products is the Agency's committee responsible for recommending orphan designation of medicines for rare diseases.
Data protection	Period of protection during which pre-clinical and clinical data and data from clinical trials handed in to the authorities by one company cannot be referenced by another company in their regulatory filings.
EEA	The European Economic Area (EEA) include all EU Member States and also Iceland, Liechtenstein and Norway.
European Joint Programme on Rare Diseases	The is co-fund between EU Member States' research funding agencies and the Commission under the EU research & innovation funding programme Horizon 2020. It aims to create an effective rare diseases research ecosystem.
EMA	The European Medicines Agency ('the Agency') is an EU agency founded in 1995 which is responsible for the scientific evaluation, supervision and safety monitoring of medicines, both human and veterinary, across Europe. (https://www.ema.europa.eu/en).
ERN	European reference networks (ERNs) are virtual networks involving healthcare providers across Europe. Directive 2011/24/EU on patients' rights in cross-border healthcare together with Delegated Decision 2014/286/EU and Implementing Decision 2014/287/EU provide for the setting up of ERNs, 24 of which were established in 2017. The purpose of these networks is to facilitate discussion of complex or rare diseases and conditions that require highly specialised treatment,

	and concentrated knowledge and resources.
Evergreening	"Evergreening" strategies extend the effective protection period and thus allow drug companies to maintain a market share after their protections expire by introducing "follow-on drugs" - those with slight changes made to them after expired protections that would normally allow generic competitors to enter the market.
Extension of marketing authorisation	A change to a marketing authorisation which fundamentally alters its terms. Such changes may concern the active substance, the strength, the pharmaceutical form and/or the route of administration.
FDA	United States Food and Drug Administration.
Generic medicine	A generic medicine contains the same active substance(s) as the reference medicine, and it is used at the same dose(s) to treat the same disease(s). The generic can only be marketed after expiry of the data and market protection.
Global marketing authorisation	A global marketing authorisation contains the initial orphan marketing authorisation and all additional indications granted to the marketing authorisation holder of the initial authorisation.
HUMN	High Unmet Medical Need
HTA	A health technology assessment (HTA) is the systematic evaluation of the added value of a new health technology compared to existing ones. It is a multidisciplinary process to evaluate the social, economic, organisational and ethical issues associated with a health intervention or health technology. The main purpose of conducting an assessment is to inform pricing & reimbursement decision-making.
Horizon 2020 (H2020)	EU Framework Programme for Research & Innovation for the period 2014-2020.
Horizon Europe (HE)	EU Framework Programme for Research & Innovation for the period 2021-2027.
IA	An impact assessment must identify and describe the problem to be tackled, establish objectives, formulate policy options, assess the impacts of these options and describe how the expected results will be monitored. The Commission's impact assessment system follows an integrated approach that assesses the environmental, social and economic impacts of a range of policy options, thereby ensuring that sustainability is an integral component of Union policymaking.

IQVIA	IQVIA is a contract research and analytical services organisation that collects data including global pharmaceutical sales data (https://www.iqvia.com/). These sales data were used for this IA.
Magistral/officinal formula	A medicinal product prepared in a pharmacy in accordance with a medical prescription or according to the prescriptions of pharmacopoeia and intended to be supplied directly to patients served by the pharmacy.
Medical condition	Any deviation(s) from the normal structure or function of the body, as manifested by a characteristic set of signs and symptoms (typically a recognised distinct disease or a syndrome).
Marketing authorisation	The approval to market a medicine in one, several or all European Union Member States.
Marketing authorisation application	An application made to a European regulatory authority for approval to market a medicine within the European Union.
Market exclusivity	The period after the marketing authorisation of an orphan medicine when similar medicines for the same indication cannot be placed on the market. Under the current legislation, the market exclusivity has a duration of 10 years.
Market protection period	Part of the regulatory protection period, supplementing the data protection period. It is the period of protection during which generics cannot be placed on the market.
Megatrends	Megatrends are long-term driving forces that are observable now and will most likely have significant influence on the future. Megatrends are closely interlinked between each other and simultaneously affect many different stakeholders. Thus, a systemic and global understanding of the issue under study is necessary to fully picture and illustrate the dynamics at stake. See also: The Megatrends Hub | Knowledge for policy (europa.eu)
Neonatology	A subspecialty of paediatrics consisting of medical care for new-born infants, especially the ill and premature.
Non-cash benefits	Non-cash or intangible benefits are benefits expected from improved actual treatment, resulting in reduced mortality, improved quality of life and time saved by informal carers.
“Off-label” use	Use of a medicine for an unapproved indication or in an unapproved age group, dosage, or route of administration. E.g. use of a medicine in children that is authorised for adults

Oncology	A branch of medicine that specialises in the prevention, diagnosis and treatment of cancer.
“On-label” use	A medicine is being used as described in the marketing authorisation.
Orphan condition	A medical condition, that meets the criteria of a life-threatening or chronically debilitating condition affecting no more than five in 10 thousand persons in the EU defined in Article 3 of Regulation (EC) No 141/2000.
Orphan designation	A status assigned to a medicine under development intended for use against a rare condition. The medicine must fulfil certain criteria for designation so that it can benefit from incentives such as market exclusivity.
Orphan indication	The proposed therapeutic indication at the time of the orphan designation. This specifies if the medicinal product subject to the designation application is intended for diagnosis, prevention or treatment of the orphan condition.
Orphan-likes	Orphan-like medicinal products to treat rare diseases which entered the EU market from the United States before 2000, when there was no special legislation in place.
Orphan Regulation	Regulation (EC) No 141/2000 on medicinal products for rare diseases
Payer	An entity responsible for financing or reimbursing healthcare e.g. national or private health insurance systems
Paediatric Regulation	Regulation (EC) No 1901/2006 on medicinal products for medicines for children
PDCO	The Paediatric Committee is the Agency's scientific committee responsible for activities associated with medicines for children. It supports the development of such medicines in the European Union by providing scientific expertise and defining paediatric need.
PIP	A paediatric investigation plan is a development plan designed to ensure that the data required to support the authorisation of a paediatric medicine are obtained through studies of its effect on children.
PUMA	The paediatric-use marketing authorisation is a dedicated marketing authorisation covering the indication(s) and appropriate formulation(s) for medicines developed exclusively

	for use on the paediatric population.
QALYs	Quality-adjusted life years refers to a measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to one year of life in perfect health. QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality-of-life score (on a 0 to 1 scale). It is often measured in terms of the person's ability to carry out the activities of daily life and freedom from pain and mental disturbance.
Rare disease	Rare diseases are diseases with a particularly low prevalence; the European Union considers diseases to be rare when they affect no more than 5 per 10,000 people in the European Union.
Regulatory data protection	Regulatory data protection refers to a period in which a generic applicant cannot refer to the marketing authorisation holder's data to obtain a marketing authorisation. For human medicines the regulatory data protection period is 8+2 years.
Repurposed medicines	Existing medicines investigated for new therapeutic indications.
R&D	Research & Development
RPV	Regulatory Protection Voucher
RSB	The Regulatory Scrutiny Board is an independent body of the Commission that offers advice to the College of Commissioners. It provides a central quality control and support function for the Commission's impact assessment and evaluation work. The Board examines and issues opinions and recommendations on all the Commission's draft impact assessments and its major evaluations and fitness checks of existing legislation.
ROI	Return on investment
SDGs	17 Sustainable Development Goals were adopted by the United Nations in 2015 as a universal call to action to end poverty, protect the planet, and ensure that by 2030 all people enjoy peace and prosperity.
SMEs	Micro, small and medium-sized enterprises
SPC	The supplementary protection certificate is an intellectual property right that serves as an extension to a patent right. The patent right extension applies to specific pharmaceutical and plant protection products that have been authorised by regulatory

	authorities.
Sponsor	Legal entity responsible for submitting an application for orphan designation to the EU.
SWD	Staff working documents are required to present the results of all impact assessments and evaluations/fitness checks.
TEV	Transferable exclusivity voucher.
Therapeutic indication	The proposed indication for the marketing authorisation. A medical condition that a medicine is used for. This can include the treatment, prevention and diagnosis of a disease. The therapeutic indication granted at the time of marketing authorisation will be the result of the assessment of quality, safety and efficacy data submitted with the marketing application.
UMN	Unmet Medical Need
Well-established use	When an active ingredient of a medicine used for more than 10 years and its efficacy and safety have been well established. In such cases, application for marketing authorisation may be based on results from the scientific literature only.

1 INTRODUCTION: POLITICAL AND LEGAL CONTEXT

In the European Union (EU) up to 36 million citizens are affected by one of the over 6,000 rare diseases[1] currently recognised. Rare diseases are those that affect less than 5 out of every 10,000 people. These diseases are often chronic and life-threatening; around 80% of rare diseases are of genetic origin and, of those, 70% already start in childhood[2]. For these patients treatment was either limited or non-existent in the 1990s. Children as a whole population group faced a similar challenge. Developing medicines for rare diseases and for children is a high-risk and expensive endeavour. In addition to limitations in scientific knowledge, developing those medicines was seen by the pharmaceutical industry as economically unattractive due to generally small market size[3]. Moreover, research and development, including conducting clinical trials, often multi-site and with small populations, is considered to be complex[4].

The 'Orphan Regulation'[5] and the 'Paediatric Regulation'[6] were adopted, in 2000 and 2006, to respond to these specific challenges. They provide developers with targeted incentives, rewards and obligations, as an add-on to the *general* EU pharmaceutical legislation[7] [8].

Over the intervening decades, a positive change resulting from these policy interventions has been observed in the Joint Evaluation conducted in 2020. While the share of orphan medicines in the total sale of branded medicines has increased worldwide from 6% in 2000 to over 16% in 2016, and it is expected to reach 21% in 2022[9] the average time to market from the date of marketing authorisation to patient *access* in the various Member States still differs enormously[10]. Furthermore, there have been wide-ranging developments and discoveries in science, which, alongside the globalisation of the pharmaceutical sector, the public health systems' sharper focus on unmet medical needs of patients and the disparities and the budgetary impacts of medicines call for revisiting the policy intervention in the area of rare diseases and medicines for children.

The revision of the EU legislation on medicines for rare diseases and medicines for children is part of the implementation of the Pharmaceutical Strategy for Europe[11], which includes the revision of the general pharmaceutical legislation. The revisions are intended to work synergistically and the interaction between them is taken into account in this impact assessment (IA), which analyses policy options for addressing the shortcomings and challenges highlighted by the Joint Evaluation and the lessons learnt from the COVID-19 pandemic.

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[1] See also Rare diseases (europa.eu).

[2] See also Section 1 of the Staff Working Document on the Joint Evaluation of Regulation (EC) No 1901/2006 on medicinal products for paediatric use and Regulation (EC) No 141/2000 on orphan medicinal products https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:52020SC0163, referred to as the "Joint Evaluation".

[3] Children are not a uniform population due to their physiological characteristics. Specific clinical trials have to be designed and conducted in preterm children, infants, toddlers, children and adolescent,

[4] Idem.

[5] Regulation (EC) No 141/2000 on medicinal products for rare diseases, https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32000R0141.

[6] Regulation (EC) No 1901/2006 on medicines for children, https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32006R1901.

[7] Legal framework governing medicinal products for human use in the EU (europa.eu).

[8] Regulation (EC) 726/2004 and Directive 2001/83/EC.

[9] OECD, New Health Technologies: Managing Access, Value, and Sustainability, 2017.

[10] Patients in Germany, the Scandinavian countries and France have access to medicines for rare diseases in a much shorter time than patients in Greece, Ireland, Bulgaria, Romania and Croatia. See also: https://doi.org/10.1016/j.jval.2018.01.007

[11] Pharmaceutical Strategy for Europe.

1.1 Legal context

1.1.1 General pharmaceutical legislation

The Orphan and Paediatric Regulations cannot be seen in isolation. They complement the provisions of the general EU pharmaceutical legislation. The general legislation harmonises the way medicines are authorised across the EU and foresees that a medicine may only be placed on the market following a positive benefit-risk assessment of its quality, safety and efficacy by a competent authority. Medicines may either be authorised centrally (CAP procedure)[12] by the European Commission on the basis of a positive scientific assessment by the European Medicines Agency ('the Agency') or nationally by an individual or a group of Member States. For orphan medicines, the use of the CAP is mandatory[13]. Such authorisation gives the right, but not the obligation, to place the medicine on the market in all Member States. Consequently, a CAP medicine is not necessarily *accessible* in all Member States. Its actual placing on the market depends on the launch strategy of companies and for most prescription medicines on national pricing and reimbursement decisions.

The general pharmaceutical legislation provides for regulatory data protection of 10 years[14] as a standard incentive for all newly authorised products, also called originators (including medicines for children and rare diseases). During that period companies cannot launch cheaper copies of medicines (generic and biosimilar)[15]. Given that the Orphan and Paediatric Regulations provide specific (additional) incentives and rewards, the system of incentives represents an important interplay between the general and the specialised legislation. To note that generic entry is also influenced by the duration of IP protection, including supplementary protection certificates ('SPC')[16]. The general legislation moreover regulates other issues like the scientific requirements for authorisation, the safety monitoring (pharmacovigilance), as well as manufacturing, distribution and advertising. Those provisions apply to all medicines, including those for rare diseases and children.

A detailed description of the EU legislative framework on medicines and the interplay between the general and specialised legislation is available in Annex 6, 7 and 12.

1.1.2 Regulation on medicines for rare diseases

The Orphan Regulation aims at enabling research, development and authorisation of new medicines for rare diseases through specific incentives ('market exclusivity').

An orphan medicine is a medicine for a life-threatening or chronically debilitating disease affecting no more than 5 in 10,000 people in the EU (prevalence criterion) or a medicine that, without incentives, would be unlikely to generate sufficient return to justify the investment (return of investment criterion). No satisfactory treatment for such diseases should exist in the EU, or, if it exists, the product should provide significant benefit to patients affected by that condition in comparison with the existing treatment.

The Orphan Regulation establishes a two-step procedure:

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[12] The CAP is laid down in Regulation 726/ 2004. Authorisation procedures - The centralised procedure (europa.eu).

[13] Medicines for children can be authorised under the CAP, but no obligation is in place. The marketing authorisation holder can decide which procedure to follow.

[14] Meaning the period of protection during which pre-clinical and clinical data and data from clinical trials handed in to the authorities by one company cannot be referenced by another company in their regulatory filings.

[15] Unless they obtain the data supporting the authorisation with their own clinical trials.

[16] They apply to specific pharmaceutical and plant protection products that have been authorised by regulatory authorities. SPCs aim to offset the loss of patent protection for pharmaceutical and plant protection products that occurs due to the compulsory testing and clinical trials these products require prior to obtaining regulatory marketing approval. See also: Supplementary protection certificates for pharmaceutical and plant protection products (europa.eu).

- **Designation prior to marketing authorisation**: a company may request at any stage of development an 'orphan designation' (recognising the potential ability of the future medicine to address a rare disease), based on an opinion by the Agency and a Commission decision. Such designation may allow developers (researchers, SMEs[17], not-for profit entities, big companies) to secure financial support for research and development (R&D), for example through the EU research framework[18] or national funding mechanisms. A designation may also help SMEs attracting risk capital provided by investors. In addition, it may enable a product to receive dedicated support from the Agency, such as scientific advice for the design of trials[19].
- **Authorisation**: if, at the time of granting the marketing authorisation, the evidence confirms continued compliance with the designation criteria, an orphan medicine will benefit from 'market exclusivity', providing a monopoly-like protection for 10 years from competition from *similar* medicines for the same therapeutic indication. The protection goes beyond regulatory protection provided by the general pharmaceutical legislation as it protects against the competition from all *similar* products, and not only against generics. The market exclusivity period may be shortened to 6 years if it is established that the criteria are no longer met, and that the product is sufficiently profitable.

1.1.3 Regulation on medicines for children

The Paediatric Regulation works with a mix of obligations and rewards. It compels companies to screen any new medicine (especially, adult medicines) for possible use in children. To compensate for the additional costs incurred[20], it provides rewards (prolongation of the duration of the supplementary protection certificate) once the obligation is fulfilled.

The Regulation requires companies at an early stage in the development of any new medicine to engage with the Agency, by either agreeing on a paediatric clinical research and development programme (paediatric investigation plan – 'PIP), or obtaining a derogation ('waiver') from this obligation. Such waivers may be granted if the product is dangerous for children, if the disease concerned does not exist in children or if the product is not expected to not bring significant benefits to children compared to existing treatments. The agreed clinical studies must be conducted in parallel with the adult studies, unless the Agency agrees that some or all of the studies with children should be conducted later. Such 'deferrals' are granted if the paediatric studies would delay the marketing authorisation for adults or if information deriving from adult studies are needed before initiating paediatric research. Once a PIP is completed and the results are included in the marketing authorisation and even if the studies show that the product is unsuitable for children, the company is eligible for one of two mutually exclusive rewards:

- An entitlement to a six-month extension of the SPC; or
- A two-year extension of the market exclusivity if the product is an orphan medicine.

Both extensions cover the *entire* product, including the "adult" part. However, the SPC extension is not automatic. An application must be filed to the national patent office and that two years before the SPC expires[21].

[17] Small and medium-sized enterprises (SMEs) are defined in the EU recommendation 2003/361.
[18] Research and Innovation, Horizon Europe.
[19] Scientific advice and protocol assistance | European Medicines Agency (europa.eu).
[20] Cost of conducting clinical studies in children and administrative costs to comply with the obligation.
[21] Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009.

To drive the development of indications for children for *existing* products, which are no longer covered by a patent (repurposing), a paediatric-use marketing authorisation ('PUMA') entitles to 10 years protection from generic competition covering the newly authorised paediatric indication[22].

1.2 Political and policy context

This initiative is part of the **Pharmaceutical Strategy for Europe** (the 'Strategy') aiming to create a future proof regulatory framework, to foster patient access to innovative and affordable medicines, to support the competitiveness and innovative capacity of the EU's pharmaceutical industry and ensure robust supply chains so that Europe can provide for the needs of its patients. It supports the EU's ambition to build a stronger **European Health Union**[23], in which all EU countries prepare and respond together to health crises, medical supplies are available, affordable and innovative, and countries work together to improve prevention, treatment and aftercare for diseases such as cancer.

Together with the revision of the general pharmaceutical legislation the review of the Orphan and Paediatric Regulation therefore aim to address similar problems and achieve common objectives: promoting innovation to better address unmet medical needs, creating an enabling environment to improve affordability and access of patients to innovative medicines and reducing regulatory burden, recognising some trade-offs between those objectives. This impact assessment takes into account this overlap in the description of the problem drivers and through aligning the methodology and the design of the options. Planned modulations to the incentives to address access and affordability in the general pharma legislation have therefore been considered when designing changes to the orphan market exclusivity and vice versa. Moreover, paediatric and orphan medicines will benefit from new instruments to support innovative products, provisions to improve access and affordability, as well as measures for simplification like an increased digitalisation of the system (such as the electronic submission of applications) introduced by the revision of the general pharmaceutical legislation.

1.2.1 Link with other initiatives

As highlighted, the Orphan and Paediatric legislation regulate only specific aspects in the life-cycle of these medicines. They can be considered as an enabling element in a broader landscape of policy interventions. Another important element in this landscape is the direct funding of **research and development**, supported through the EU Horizon 2020 and Horizon Europe[24] programmes. From 2007 to 2020, the EU supported research on rare diseases substantially, with more than €2.9 billion attributed to over 1000 R&I projects (approximately €205 million/year from 2007-2013 and €215 million/year from 2014-2020[25]). Under these programmes, funding is mostly allocated to pre-competitive research for catalysing innovation in drug development in the medium and long term. In this way, it is expected that these public investments provide the science needed from which new orphan medicines may be discovered later. In addition, the European Joint Programme on Rare Diseases[26], co-funded between Member States and the Commission, also aims to contribute to more and better research on rare diseases. The European Commission also foresees under its Horizon Europe and health research priority, a European Partnership co-fund on Rare Diseases[27], which should be operational by mid-2024 and it will bring together a broad range of research and

[22] A generic medicine is a medicine that is developed to be the same as a medicine that has already been authorised. Its authorisation is based on efficacy and safety data from studies on the authorised medicine. A company can only market a generic medicine once the protection periods for the original medicine has expired.
[23] The European Health Union was announced by Ursula von der Leyen, President of the European Commission, in 2020, European Health Union | European Commission (europa.eu).
[24] EU rare diseases research
[25] Data received from DG RTD.
[26] The European Joint Program on Rare Diseases.
[27] Draft Proposal for a European Partnership under Horizon Europe – Rare Diseases, 18/02/2022.

innovation actors. Moreover, the EU RD Platform[28] which tackles the fragmentation of rare disease patients data contained in scatted registries across Europe, provides a Pan-European infrastructure to securely access and share patient data for advancing clinical research and healthcare delivery.

The EU's Mission on Cancer[29] together with the initiatives under **Europe's Beating Cancer Plan**[30] aim at boosting research and development of novel treatments for cancer but also to improve its screening and early detection. These will complement the paediatric regulation ensuring that cancer, which is the first cause of death by disease post infancy, will be tackled in a multi-facet way, from prevention and diagnosis, to treatment to quality of life of patients.

The new **Clinical Trials regulation**[31] allows as of 2022 a more efficient process for the approval of multinational trials through a single application and a common assessment. This facilitates the conduct of trials in small populations like orphan medicines and children, which are often multi-country trials. The Regulation will also increase transparency on which trials are ongoing in the EU and on their results.

Not only basic research but also the early and correct diagnosis of a rare disease is a challenge, which cannot be directly addressed by the Orphan and Paediatric Regulation. The **European Reference Networks** (ERNs)[32] support the diagnosis and treatment of patients suffering from rare diseases and help to connect experts and health professionals in a virtual network.

The **European Health Data Space**[33] will provide a common framework across Member States for the access to high-quality real world health data. The data that will become accessible are expected to allow progress in research and development of medicines. The health data space is expected to benefit in particular small patients' populations, such as the people living with a rare disease. This is due to the fact that at the moment health data of such population groups are scattered across Member States.

The **Intellectual Property Action Plan**[34] under the Industrial Strategy[35] includes the modernisation of the system of supplementary protection certificates (SPC) in the form of a "Unitary SPC"[36] which does not intend to modify the maximum period of a SPC, but may lead to wider coverage of SPCs (the major reward for developers for medicines for children).

1.2.2 The pharmaceutical ecosystem

The orphan and paediatric legislation intervene in a complex ecosystem. On the *supply side*, the pharmaceutical sector is characterised by two main types of companies: originator companies and generic companies[37]. Originator companies can range from 'Big Pharma' to biotech and SMEs concentrating on certain niche products. In the orphan sector, 42 % of the authorised products have been *developed* by SMEs[38] although the number of marketing authorisation holders among SMEs tend to be lower as they may have been acquired by larger pharmaceutical companies during the

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[28] https://eu-rd-platform.jrc.ec.europa.eu/_en
[29] Implementation Plan, European Missions – Cancer.
[30] Communication - Europe's Beating Cancer Plan.
[31] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC.
[32] Overview European Reference Networks (europa.eu); ERNs are regulated by Directive 2011/24/EU.
[33] COM(2022) 197 final.
[34] COM(2020)760 final.
[35] COM(2021) 350 final.
[36] Medicinal & plant protection products – singles procedure for the granting of SPCs
[37] Generic companies 'copy' a product that has already been authorised, once protection periods have expired (at a lower price, therefore addressing affordability issues in health systems).
[38] Data from EMA.

development phase of the orphan product.[39]. Generally, pharmaceutical companies in the EU are a large funder of pharmaceutical R&D, making the biggest contribution to research investment in 2019, with over €37 billion. The sector provides 800 000 direct jobs and a €109.4 billion trade surplus[40]. The *demand* side of the pharmaceutical sector is rather unique as it is characterised by a complex ecosystem of agents including patients, doctors, hospitals, health technology assessment bodies, and payers. For prescription medicines, the final consumer (i.e. the patient) differs from the decision maker (generally the prescribing doctor) and very often also from the payer (generally in the EU the national health system, and ultimately the taxpayers)[41].

A description of the pharmaceutical ecosystem is provided in Annex 7.

1.2.3 International context

Medicines development is global. R&D investment and regulatory frameworks are therefore influenced by developments in other regions. The structural features of the US regulatory system for orphan and paediatric medicines are very similar to the EU system and they have influenced each other over the years. However, differences exist with regard to other support schemes and the demand/access side, which make the US market very attractive for developers.

For *orphans*: the US legislation provides seven years of market exclusivity, which is lower than in the EU. But the US has higher annual figures for both designations and marketing authorisations for orphan medicines. This is mostly explained by tax incentives (50% of development cost is tax deductible in the US) and by differences in eligibility criteria for obtaining an orphan designation. In the EU, rare diseases are defined as affecting smaller numbers of people than in the US. Some medicines not eligible for orphan designation in the EU are thus considered orphan in the US. Moreover, in the EU the eligibility criteria are checked again during the marketing authorisation stage, leading to some products losing their orphan status as they can no longer demonstrate their significant benefit. This is not the case in the US.

For *paediatrics*: similar to the system in the EU the US also requires companies to conduct paediatric study programmes. Their completion is rewarded with an additional protection period (6 months extension of the existing patent or exclusivity – same as in the EU). The number of medicines for children authorised is very similar between the EU and the US and it is 6 times higher than in Japan where no paediatric legal framework exists and double compared to Canada where a legislative framework exists but it is not compulsory.

There is strong global collaboration between EMA and US Food and Drug Administration (FDA) both in the areas of orphans and paediatrics, and together with other non-EU regulators.

Interestingly, also in the US a discussion gains pace pointing to changes in the orphan medicine market, where some high expenditure orphan medicines have generated significant revenues putting into question the (continued) existence of the general market failure that was at the origin of the policy intervention[42].

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[39] A good example of an initially small SME, developing medicinal products, is Shire. It came to life as a start-up in 1986 and was involved in the development of a wide range of medicinal products. Shire began broadening its scope into rare diseases with the acquisition of TKT (an orphan drug company) in 2005. It continued acquiring other pharmaceutical companies and forging partnerships until Takeda took over Shire in 2018 in a $62 billion acquisition. Before this acquisition of Shire, roughly a third of Takeda's experimental drugs carried an Orphan Drug Designation, while adding Shire took that figure up to roughly 50% of Takeda's pipeline of orphan designations. See also: A history of Shire (pharmaphorum.com) and Shire deal done, Takeda turns to task of forging top pharma | BioPharma Dive

[40] Section 1 of the Pharmaceutical Strategy for Europe.

[41] European pharmaceutical research and development, European Parliament Research Service, p. 7.

[42] High-expenditure Medicare drugs often qualified for Orphan Drug Act incentives designed to encourage the development of treatments for rare diseases, US Department of Health and Human Services.

Further information on the international context can be found in Annex 8.

1.2.4 United Nations' Sustainable Development Goals (UN SDGs)[43]

This initiative is in line and supports the achievement of the UN SDGs, in particular SDG 3 ('ensure good health and well-being at all ages') by addressing the insufficient development of medicines in areas of unmet medical needs. The objectives and proposed measures aimed at tackling unmet medical need, affordability and unequal access to medicines across the EU are linked to SDG 3. More details are provided in Annex 3.

1.2.5 COVID-19

The COVID-19 crisis has impacted EU health systems. Most of the respondents to the public consultation[44] considered that global attention and resources rapidly shifted towards COVID-19 and R&D efforts in the areas of medicines for rare diseases and children were reduced. On the other hand, more innovative ways to involve children in clinical trials and increased flexibility and efficiency in conducting them may have positive impacts. COVID-19 also showed the possibility for an acceleration and streamlining of some regulatory procedures (e.g. PIP agreements and compliance checks for COVID-19 vaccines). These learnings inform some of the proposed changes to streamline procedures and other simplifications which are examined in this intervention.

2 PROBLEM DEFINITION

2.1 What are the problems?

The Joint Evaluation showed that both Regulations have contributed to fostering the development and authorisation of medicines for rare diseases and children in the past 20 years. They have redirected private and public investments towards these previously neglected areas and favored the creation of an EU research environment for both areas. However, the interventions were not the only factor contributing to these results. They represented an important enabler complementing other policies like increased research funding[45].

The number of medicines for patients with rare diseases has increased[46] and have reached a higher number of patients. Similarly, the number of clinical trials involving children and, consequently, the development of new medicines for them increased. Companies consider now new paediatric developments as an integral part of pharmaceutical development

Despite these positive developments, four main problems have been identified[47]:

1. Medical needs of patients with rare diseases and children are not sufficiently met;
2. Affordability of medicinal products is a challenge for healthcare systems;
3. Unequal access to medicines across the EU;
4. The system caters insufficiently for innovation and creates unnecessary burden.

These problems ultimately impact patients but also concern a broader range of stakeholders including national public authorities, civil society and the pharmaceutical industry.

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[43] THE 17 GOALS | Sustainable Development (un.org).
[44] Medicines for children & rare diseases – updated rules (europa.eu).
[45] See also Sections 1.2 and 1.3 of this SWD.
[46] The Joint Evaluation (Section 6) found that during the time period 2000-2017, 142 orphan medicines have been authorised. These medicines have helped up to 6.3 million European patients.
[47] The problems were identified in the main findings of the Joint Evaluation (Section 6) and are common to orphans and all other medicines covered by the general pharmaceutical legislation.

The findings from the evaluation were confirmed by the feedback received on the inception impact assessment[48], the public and targeted surveys and the desk analysis conducted in the course of this IA. The summary below provides updated information on the problem definition further to what was presented in the Joint Evaluation.

2.1.1 Medical needs of patients with rare diseases and children are not sufficiently met

The Orphan Regulation fostered R&D in the field of medicines for rare diseases in the EU. To date, the Commission has authorised more than 200 medicines for rare diseases and designated around 2000 molecules in development. However, 95% of the over 6000 recognised rare diseases still have no treatment option[49] and for those that have, the majority of the treatments are symptomatic and not curative. Both areas can consequently be considered as areas of *high* unmet medical need (HUMN) for patients suffering from rare diseases. The current system has no instruments to channel developments in certain areas of particular need for patients. Investors therefore tend to prioritise the most commercially lucrative orphan disease areas[50], as well as areas where risks of failure due to insufficient scientific knowledge is less, rather than those with higher public health benefits.

Concerning medicines for children, developments are still driven by *adult* developments. When the therapeutic need for adults diverge from the ones of children, like in the case of paediatric cancers, mental and behavioral disorders or treatments for neonates, the number of treatments available is limited[51]. Furthermore, currently, a PIP is not required where an adult product is intended for a disease that does not exist in children. However, such a product could, on the basis of scientific evidence, also be effective against a different disease. This may for example be a product developed to treat an adult cancer (non-existing in children) that could also be effective to treat a different type of cancer in children.

All stakeholders agreed that developments in areas of UMN for patients should be better supported, even if some representatives from public authorities raised concern that such products should not come with excessive costs for their health systems.

2.1.2 Affordability of medicines is a challenge for health systems

Pricing and reimbursement decisions and pharmaceutical expenditure are national competences and outside the scope of the orphan and general pharmaceutical legislation. Decisions vary across the EU. However, under national legislation, orphan medicines often benefit from separate budgets, lower requirements for data for pricing and reimbursement decisions and substantial willingness to pay, sometimes at a very high cost, often under pressure by advocacy groups and public opinion[52]. To compensate for uncertainties with regard to cost-effectiveness existing at the time of Health Technology Assessment, some Member States have put in place managed entry agreements (MEAs)[53]. The separate budgets for orphans may allow companies to charge higher individual prices for their orphan products, although MEAs can reduce the prices, making coverage and payments to companies or rebates paid by companies conditional on product performance[54].

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[48] Inception impact assessment.
[49] Section 3 of the Joint Evaluation.
[50] Including in areas where an active ingredient of a medicine has been used for more than 10 years and its efficacy and safety have been well established. In such cases, the application for marketing authorisation may be based on results from the scientific literature only (but currently still gets a market exclusivity of 10 years) – well established use.
[51] 10 years EMA technical report to the Commission, table 11.
[52] Section 5.1 of the Joint Evaluation.
[53] Agreements between pharmaceutical companies and healthcare payers that allow for coverage of new medicines while managing uncertainty around their financial impact or performance. See also: HTA Overview (europa.eu).
[54] OECD Health Working Papers No. 115.

The average list price of new medicines is fast increasing, especially for orphan medicines[55]. The consequences of high prices are affordability problems for patients and sustainability of health systems. Pharmaceutical expenditure in Europe is largely subsidised by national health systems in order to ensure the adequate provision of medicines to all their respective citizens. Orphan medicines did not always have a measurable impact on public health budgets; high individual treatment prices coupled with very small patient populations had an almost invisible effect at systemic level. However, the last decade brought an increasing number of new orphan medicines with very complex technology (CAR-T cell therapies, gene-edited therapies) and 6-7 digit price tags[56]. This is not only a problem in the EU, as the US is facing the same issue[57].

Prices for medicine vary significantly between Member States. For a sample of medicines, it was also shown that list prices were the highest in Germany and the lowest in many different EU countries but never in the ones with lower GDP per capita like Bulgaria or Romania[58].

Overall, the annual total expenditures on healthcare in the EU is around 10% of GDP[59] and this pharmaceutical spending specifically puts pressure on health systems. Medicines in the hospital account for over 20-30% of hospital expenditures and are growing[60].

The public debate is increasingly focused on medicine prices. Although the discussion is not restricted to orphan medicines, such products have received particular scrutiny, given the market exclusivity offered. In addition, it has been observed that some producers substantially increased the price of newly-authorised orphan medicines that were previously available to patients as a magistral or officinal formula (well-established use[61]) at a much lower price[62]. These price increases seem to bear no relation to actual R&D costs which is normally lower for well-established use medicines. The latter accounted, together with so called repurposed products[63], for 19% of orphan medicines in the EU[64].

Furthermore, an orphan medicinal product can currently be authorised for several orphan indications, leading to *separate* and consecutive 10-years of market exclusivity protection for each new indication authorised[65]. This delays the on-label use of generic and biosimilar products for those authorisations.

Generic and biosimilar entry and competition is an important factor to achieve lower prices, broadening patients' access and alleviating healthcare costs. Generic entry does however not always happen, due to the usually small market size for orphan products (fewer patients), which can make the market commercially less attractive for generic manufacturers. Looking at the 36 products (out of 190 orphan products in the period 2000-2020) for which the market exclusivity already expired, 11 saw at least one generic competitor with sales.

Concerning medicines for children, their price depends on the price of the "adult" product. No specific issues on high prices of medicines only for children were identified. However, the rewards

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[55] OECD, New Health Technologies: Managing Access, Value, and Sustainability, 2017
[56] OECD, New Health Technologies: Managing Access, Value, and Sustainability, 2017
[57] Orphan drugs in the United States, IQVIA.
[58] Zaprutko T. et al. Affordability of medicines in the European Union. *PLoS One*. 2017;12(2):e0172753.
[59] Eurostat System of Health Accounts, 2019 data. Recent joint projections from the European Commission and Member States (2021) indicate that public spending on healthcare, as a share of GDP, is projected to increase by a factor of 1.1 between 2019 and 2040.
[60] European Commission, State of health in the EU: companion report 2019 (ISBN 978-92-76-10194-9).
[61] I.e. when an active ingredient of a medicine has been used for more than 10 years and its efficacy and safety have been well established. See also: Well-established use | European Medicines Agency (europa.eu)
[62] ACM imposes fine on drug manufacturer Leadiant for CDCA's excessive price | ACM.nl
[63] Existing medicines that are investigated for new therapeutic indications.
[64] See also Section 5.2 of the Joint Evaluation; Data until 2018.
[65] So called indication stacking. See also Section 5.2.3. of the Joint Evaluation.

granted in accordance with the paediatric Regulation (SPC prolongation) may have the effect of delaying generic entry for the adult products and consequently on their affordability.

The rising costs of medicines were identified as key concerns for academics, healthcare professionals, public authorities and civil society stakeholders.

2.1.3 Unequal access to medicines across the EU

All consulted stakeholder groups[66] agree that patients' access to authorised medicines is a major issue. Out of the 190 **orphan** medicinal products developed and authorised in the 2000-2020 period, data were collected for 155 of them[67]. It was found that only about half of them are currently accessible to patients in a majority of Member States. Moreover, patient access to orphan medicines varies considerably between Member States. Germany, France or Italy for instance have a high market uptake, with more than 100 medicines for rare diseases available. On the contrary, countries like Lithuania, Bulgaria or Ireland had less than 50 orphan medicines available.[68] Compared with standard medicines, access is worse for orphan medicines[69].

The launch of an indication or medicine **for children** is often linked to the launch of the corresponding adult product. It has been observed that companies tend to rely on a staggered roll-out of any new product for adults across the EU, resulting in delays until the product for children is accessible[70].

According to all stakeholders consulted, enabling access to affordable medicines is among the areas where the EU pharmaceutical legislation has been less effective.

A description on the EU system for pricing and reimbursement is provided in Annex 10

2.1.4 The system caters insufficiently for innovation and creates unnecessary burden

Advances in science, such as advanced therapy medicinal products, personalised medicine approaches[71] and the use of biomarkers[72] have already allowed to better target treatments for patients suffering from a rare disease[73]. At the same time, these new products have challenged the current system of orphan designation, which relies on criteria which must be met if a product is to receive an orphan designation[74].

The Paediatric Regulation obliges to define at a very early stage the full clinical development plan for paediatric medicines. However, for innovative paediatric products, a detailed development plan is often decided step by step while clinical data are collected, therefore the legislation create the need to frequent modifications of the agreed PIPs causing increased administrative burdens for applicants and delays in the completion of the PIP and consequently of the authorisation of the use of the medicine in children. Moreover, the provisions on medicines for children allow to exclude from the obligation to conduct clinical studies in children certain medicines developed for diseases

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[66] Synopsis report (Annex 2 to this SWD) and Impact assessment on the general pharmaceutical legislation.
[67] Based on analysis of the IQVIA data covering the availability of medicines for rare diseases across 24 Member States
[68] See also Section 5.1.2 of the Joint Evaluation.
[69] Our findings in Section 6.2 show that orphan medicines become accessible within 10 years of authorisation for a *smaller* proportion of the EU population and that the pace is slower than for non-orphan medicines.
[70] 10 years of the EU Paediatric Regulation (report from the Commission to the European Parliament and the Council (COM(2017) 626, Section 3). Kyle, 2019, Bergmann et al., 2016; Ferrario, 2018
[71] Personalised medicine | European Commission (europa.eu)
[72] Meaning a biological molecule found in blood, other body fluids, or tissues that can be used to follow body processes and diseases in humans and animals. See also: Biomarker | European Medicines Agency (europa.eu).
[73] Section 5 of the Joint Evaluation.
[74] Article 3(1) of the current Orphan Regulation; the criteria for designation should ensure that only products addressing a rare disease fall under the scheme.

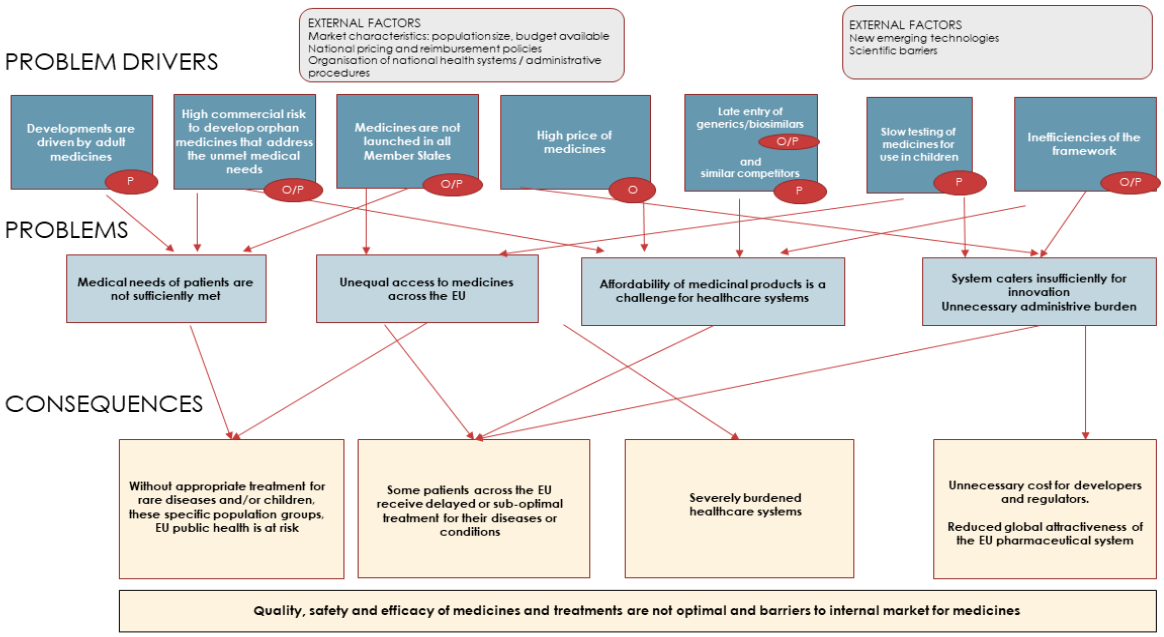
that are exclusive to adults. However, some of those medicines, in view of their mechanism of action[75], may be promising for the treatment of certain diseases in children and therefore should be researched further. This is often the case for anti-cancer medicines. Patient associations and healthcare professionals were specifically concerned about this issue[76].

Concerning **inefficient procedures**, both the Orphan and the Paediatric Regulations rely on certain procedures (e.g. for the orphan designation and the agreement on a PIP) that sometimes proved to be burdensome and inefficient leading to delays in the authorisation of a product[77]. In addition, the paediatric regulation offers 6 months SPC extension for completing PIP, and for orphan medicines 2 years of market exclusivity extension. From the entry into force of the Paediatric Regulation up to 2020, only 11 of these market exclusivity extensions were granted. The system has allowed some companies to game the system: there have been cases where companies have abandoned the orphan status of their product at the moment of marketing authorisation in order to benefit from the 6 months SPC extension. This has created a system which made it difficult for generic producers to know exactly when the paediatric protection would expire and consequently to plan accordingly.

2.2 What are the problem drivers?

Many of the drivers and problems tackled with this initiative are linked with the ones addressed in the review of the general pharmaceutical legislation. Table 1 below presents the interconnections between the drivers, problems and consequences underlying the revision of the general pharmaceutical legislation and the revision of the legislation for rare diseases (O) and children (P):

Table 1: Overview of drivers, problems and consequences[78]



[75] Article 11 of the Paediatric Regulation, provides that the obligation to conduct a PIP is waived when the medicinal product in intended for a disease which only occurs in adults.
[76] See also Annex 2 of this SWD.
[77] Section 5.2.6 of the Joint Evaluation.
[78] Red bubbles indicate the issues which are specific to the revision of the legislation for medicines for children and rare diseases. Only problems relevant for orphan and paediatric medicines are presented in the table.

2.2.1 Driver 1: Developments are driven by adult medicines

The paediatric Regulation has been successful to steer paediatric clinical research but as shown into the evaluation, medicines' development remains driven by adult needs. Limited developments are seen in areas where the medical needs of children and adults differ (for example, neonatology and certain types of paediatric cancers).

2.2.2 Driver 2: High commercial risk to develop and bring to the market new medicines that address unmet medical needs

Developing medicines for rare diseases and children is often more complex and riskier than for other medicines. Due to their low prevalence, rare diseases face a scarcity of scientific knowledge and clinical trials need to be conducted across several Member States[79]. Moreover, children cannot be considered as a homogeneous group as they cover preterm newborn to adolescents with different physiological characteristics. This results in more complex clinical trials and specific product formulations.

While investment risks and expected financial return may vary significantly, the Regulations only have one set of incentives and rewards[80]. This lack of differentiation does not necessarily direct investments in rare or paediatric diseases where the need is highest. Companies have focused primarily on orphan medicines with the highest expected return on investment and for which science has already evolved, as demonstrated by a clustering in certain diseases. Of all authorised orphan medicines between 2000 and 2017, 72% targeted diseases that have at least one other authorised treatment available[81]. While multiple treatment options can benefit patients and increase competition, development also needs to be directed into areas where there are no authorised treatments at all. Regarding medicines *for children*, it was shown that investments are still smaller when compared to the ones into adult medicines[82]. The constraints and difficulties to fully respect all safety requirements during clinical trials for such small but fragile population may explain this tendency[83].

2.2.3 Driver 3: Medicines are not launched in all Member States

The **Orphan Regulation**, like the general pharmaceutical legislation, does not impose any obligation on marketing authorisation holders to launch an authorised product in all Member States nor puts any specific requirements when withdrawing them for commercial reasons[84]. It only allows competitors to break the market exclusivity if they can demonstrate that the orphan product is not delivered in sufficient quantities.Pharmaceutical companies tend to favor the initial launch of the product in a limited number of Member States[85] and begin negotiations with Member States that may grant a higher price and have a higher 'willingness to pay'[86] (often countries with the highest GDP per capita[87]). Furthermore, the timelines for completing pricing and reimbursement decisions and HTA assessment vary considerably between Member States with some being overly delayed[88]

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[79] EURORDIS. Final Conclusions and Recommendations of the Pharmaceutical Forum.
[80] See also Sections 1.2.3 and 1.2.4 of this SWD.
[81] See also Section 6 of the Joint Evaluation.
[82] See also Section 6 of the Joint Evaluation
[83] Vieira I. et al, Paediatric Medicines - Regulatory Drivers, Restraints, Opportunities and Challenges. J Pharm Sci. 2021 Apr;110(4):1545-1556. Available at: https://doi.org/10.1016/j.xphs.2020.12.036.
[84] The number of reimbursed orphan medicines at present varies greatly across the EU. See also: Check et al. (2019), 'A Review of Rare Disease Policies and Orphan Drug Reimbursement Systems in 12 Eurasian Countries', Front Public Health, 2020 Jan 28; 7:416, DOI: 10.3389/fpubh.2019.00416, available at https://pubmed.ncbi.nlm.nih.gov/32117845/.
[85] Section 5.1.2 of the Joint Evaluation.
[86] Meaning the maximum amount of money that may be contributed to receive an extra service or treatment (an important approach in economics for valuation of health benefits and medication programs).
[87] Statistics | Eurostat (europa.eu).
[88] Pharmaceutical Sector Inquiry Final Report – July 2009.

[89]. The recently adopted HTA Regulation, providing for joint assessments may improve the situation, but this also underlines that some problems cannot be addressed by the orphan legislation itself.

The Paediatric Regulation includes very limited provisions to ensure that patients have access to an authorised paediatric medicine. An exception is that when a PIP has led to the authorisation of a paediatric indication for a product already marketed for other indications, such indication has to be placed on the market in the Member States within a two-year period. Furthermore if a company intends to withdraw the medicine which had benefitted from the reward, it has to offer the marketing authorisation to a competitor first. However, access for patients of these products across Member States is not uniform and is influenced by launch decisions of the equivalent medicine for adults. Also, there are currently no tools to influence the launch of adult product under the general pharmaceutical legislation[90].

2.2.4 Drivers 4 and 5: High prices and costs of innovative medicines and delay of entry of generics/biosimilars and similar products

Companies often explain increasing prices of innovative medicines by the increase of R&D costs[91] and small targeted populations are often recalled as a reason for high prices of orphan medicines, even if a recent study found that the clinical costs per approved orphan medicine is lower and in certain cases half that of a non-orphan medicines[92]. Orphan medicines are the source of the fastest growth of the general spending on pharmaceuticals both in the EU and the US[93]. Seen against a growing number of orphan medicinal products on the EU market, limitations in national health budgets have also influenced uptake and patient access[94].

While the new EU Regulation on Health Technology Assessment[95] is expected to improve the situation in terms of speeding up market access through accelerated availability of joint relative efficacy assessments[96], it does not directly tackle any financial burden or necessary changes to national price negotiations and reimbursement models. Those decisions are based on national policies and are outside the scope of EU legislation and this revision[97]. Nevertheless, the regulatory protection periods and the market exclusivity provided by EU legislation give a monopoly power to companies that can influence negotiations and contribute to high prices[98]. Furthermore, the fragmented and non-transparent EU medicines market leads to sometimes significant differences in prices for the same medicine in different countries. The sheer monitoring of the price differences is a challenge in itself, as official list prices do not reflect confidential rebates that can go up to 30-40% of the price[99].

Generics and biosimilars normally reduce the prices. Delayed entry of generics and biosimilars therefore has a negative impact on patient access and affordability. Apart from the small size of the

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[89] See also Annex 2 of this SWD (stakeholder consultation).
[90] Lepola P., Wang S., Tötterman, A.M., et al. (2020). Does the EU's Paediatric Regulation work for new medicines for children in Denmark, Finland, Norway and Sweden? A cross-sectional study, BMJ Paediatrics Open.
[91] OECD, New Health Technologies: Managing Access, Value, and Sustainability, 2017.
[92] Jayasundara K, Hollis A, Krahn M, et al.. Estimating the clinical cost of drug development for orphan versus non-orphan drugs. Orphanet J Rare Dis. (2019) 14:12. 10.1186/s13023-018-0990-4 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
[93] Orphan Drug Report 2022, Evaluate Pharma.
[94] See also Section 2.1 of this SWD.
[95] Regulation (EU) 2021/2282 on health technology assessment (HTA)
[96] Section 6.3.1. of the Commission Impact Assessment 'Strengthening of the EU Cooperation on Health Technology Assessment (HTA)' - SWD(2018) 41 final.
[97] See Section 1 "Policy context" of this SWD.
[98] European pharmaceutical research and development. European Parliament Research Service.
[99] Health at a Glance: Europe 2022 – Pharmaceutical expenditure, OECD

population, there are some additional regulatory hurdles for generic and biosimilar entry due to the design of the Orphan Regulation. Currently, market exclusivity does not allow for generics to *apply* for market authorisation before its expiration, which means an additional windfall protection and delay for generics beyond the 10 years. In some cases a second generation orphan medicine is even blocking generic copies of the first generation product, namely where the first and second generation product were considered similar and as market exclusivity protects against market entry of similar products. Furthermore, new indications in a different orphan disease for an already authorised product lead to a new 10 year market exclusivity period for this indication, meaning that generic/biosimilars cannot copy the entire product but only partially for considerable time[100].

2.2.5 Driver 6: Slow testing of medicines for use in children

The PIPs have to be conducted in parallel with the adult studies, unless the Agency agrees that some or all of the studies with children should be conducted later[101]. Such 'deferrals' are granted for instance if the paediatric studies would delay the 'adult' authorisation or if information deriving from adult studies are needed before initiating paediatric research. Currently over 80% of PIPs include full or partial deferrals, some of them are very long. This results in a delayed access of adapted medicines for children.

2.2.6 Driver 7: Inefficiencies in the legal framework

The development of innovative therapeutic solutions has created some regulatory challenges[102] and this results in the current system not being able to cater for these innovations which could benefits patients with rare diseases and children. Regarding *orphan* medicines, certain scientific developments have challenged established concepts used in the orphan legislation. Current legal definitions are directly linked to the concept of a disease and to the prevalence of the condition. It needs to be verified whether these legal provisions are still fit for purpose in view of new scientific developments[103].

Regarding *paediatric* medicines, the ability to better understand the molecular causes of diseases could allow to identify if certain adult products could be also useful to treat a different paediatric disease. This is particularly relevant in oncology. However, the current Regulation does not allow to explore these potential opportunities, as it waives the obligation for a PIP for products developed for a disease that does not exist in children, thus hampering innovation[104].

Furthermore, for orphan and paediatric products the assessment pathway is currently quite complex. Such products may be assessed by up to four Agency committees: the Committee for Orphan Medicinal Products (COMP) for the orphan designation, the Paediatric Committee (PDCO) for approval of the PIP, the Committee for Medicinal Products for Human Use (CHMP) for the benefit-risk assessment for marketing authorisation and in the case of ATMPs, the Committee for Advanced Therapies (CAT). While the remit of the various committees is clear, inconsistencies of outcomes, data needs and timelines were identified[105]. In addition, orphan designations are granted through a

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[100] These additional market exclusivities means that generic medicines can enter the market in the first indication, but cannot be used in subsequent indications. This indication protection is not as strong as the initial exclusivity, because the doctors and health payers are aware that the generic molecules work the same way in all indications. At the same time, the market exclusivity holder has limited capability to demand a price premium: if the price gap with generics is too large, doctors may prescribe the generic version "off-label" for the protected indication. 16% of orphan medicines currently have multiple orphan indications, and on average they extend the first market exclusivity by 4.2 years.

[101] Article 20 of the Paediatric Regulation.

[102] See also Section 2.1 of this SWD.

[103] Sections 5.3 and 6 of the Joint Evaluation.

[104] Idem.

[105] Idem.

Commission decision, while PIP agreements are directly adopted by the Agency, creating incoherence in pre-authorisation decision-making.

2.3 How likely is the problem to persist and how will the problem evolve?

The Joint Evaluation[106] and the analysis conducted - based on information collected from the Agency and via the consultation process - suggest that the above drivers and problems would continue to exist. While the current Regulations are expected to contribute to an overall *increase* of medicines for rare diseases and for children, this increase is insufficient to rapidly provide treatment solutions for all patients and address unequal access to medicines across the EU. The entry of generic and biosimilar products will remain slow as an application for these products can be submitted only on the day the exclusivity period of the orphan medicine expires. Delayed generic entry will in turn continue to negatively impact affordability of orphan medicines. Some national initiatives, like national orphan plans, try to offer solutions to support rare disease research and product availability on a national level; they have grown substantially since 2009[107] [108]. However, there is no indication that R&D investments will focus more on areas of unmet medical need. Similarly the existing design of the rewards will not prioritise product development in areas of specifically paediatric needs where these differ from the needs of adults. The HTA legislation is expected to provide a positive impact on patient access to new medicines by supporting Member States in taking more evidence-based and timely decisions. A forthcoming revision of the SPC legislation aims to put in place a unitary SPC and/or a centralised procedure for granting national SPCs[109] which is expected to simplify the procedures for obtaining the SPC extension for the completion of the PIPs.

2.4 Megatrends

The persistence of the problem is also confirmed by some of the megatrends identified by the EU Joint Research Centre[110] as part of its foresight activities[111]. Out of the 14 megatrends, four trends are likely to have a strong impact on the aforementioned problems. These trends would also pose additional strain on health systems and research needs and budgets would need to be prioritised between the different challenges.

Megatrend 1 and 4: Shifting health challenges, climate change and environmental degradation. This overarching topic includes trends ranging from the digitalisation of society to demographic changes or environmental challenges. Even though science and technology enable us to live longer, the rise of new diseases due to anthropogenic causes and demographic changes will create a new burden for public health. The Covid-19 crisis best pictures this situation. The impact of changing climate patterns on public health is another example. It is therefore crucial to create a more agile and flexible legislative framework ready to adapt to future challenges and to simultaneously maintain its objectives in terms of research and innovation to ensure development in areas of greatest unmet medical needs and availability and accessibility across Member States.

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[106] Section 6 of the Joint Evaluation.

[107] The EPSCO Council issued a recommendation in 2009 for Member States to create and adopt a plan focused on rare disorders by the end of 2013. Twenty-five Member States followed this recommendation.

[108] Twelve countries (Croatia, Czech Republic, Finland, France, Hungary, Latvia, Luxembourg, Portugal, Romania, Slovak Republic, Slovenia, Spain) have an ongoing national plan/strategy with a specified time-period. Austria, Belgium, Cyprus, Lithuania, and Germany have an 'open-ended' national plan/strategy. In seven countries, the national plan/strategy is expired: Bulgaria (expired in 2013), Denmark (apparently expired 2019), Estonia (expired in 2017), Greece (expired in 2012), Ireland (expired in 2018), Italy (expired in 2016), and the Netherlands (expired in 2018).

[109] Medicinal & plant protection products – single procedure for the granting of SPCs (europa.eu).

[110] The Megatrends Hub, https://knowledge4policy.ec.europa.eu/foresight/tool/megatrends-hub_en#explore.

[111] Foresight is the discipline of exploring, anticipating and shaping the future to help building and using collective intelligence in a structured, and systemic way to anticipate developments. Strategic foresight seeks to embed foresight into EU policy-making. See also: https://ec.europa.eu/info/strategy/strategic-planning/strategic-foresight_en.

Megatrend 2: Accelerating technological change and hyperconnectivity. Increasing technological developments are changing the way we live, but also the nature and speed of new discoveries. In the field of public health, it implicates new ways to generate health data at individual level to develop more personalised treatments based on patients' needs. Technological changes are fundamental in the area of research and innovation to maintain scientific developments, especially in areas where the population affected is small and scattered between several Member States. There are also great potentials in connecting datasets and advanced analytics – in particularly to identify new treatments via mechanism of action research or assess the safety and efficacy of orphan and paediatric medicines based on real world evidence. Administrative burden and inefficient procedures could be improved thanks to the use of technological tools.

Megatrend 3: Increasing demographic imbalances. Global population is growing and age structures more uneven. Especially in Europe, population is ageing and birth rates are declining. Consequently the population of children becomes smaller[112]. This development is expected to make more difficult the organisation of clinical research involving children and would also impact the return on investment for pharmaceutical companies.

3 WHY SHOULD THE EU ACT?

3.1 Legal basis

The Orphan and Paediatric Regulations are based on Articles 114(1) and 168(4)(c) of the Treaty on the Functioning of the European Union (TFEU).[113] These provisions give the EU the mandate to adopt measures which have as their object the establishment and functioning of the internal market (Article 114(1) as well as measures setting high standards of quality and safety of medicinal products (Article 168(4)(c)). Any future legislative proposals, supported by this impact assessment, will be based on Articles 114(1) and 168(4)(c) TFEU. It will also be aligned with Article 35 of the EU Charter of Fundamental Rights that provides that the Union is to ensure a high level of human health protection in the definition and implementation of Union policies.

3.2 Subsidiarity: Necessity of EU action

Diseases do not know borders. Ensuring the availability of medicines for rare diseases and for children affect all Member States. As such, this can effectively be regulated only at EU level. The authorisation of medicinal products, including orphan medicines and medicines for children, is fully harmonised at EU level. Member States cannot introduce specific provisions at national level in this field. A harmonised approach at EU level also provides greater potential for incentivising the development in the area of unmet needs. The market for individual orphan medicines is small even in larger EU Member States. Any national initiative would need to provide substantial incentives for developers to change their investment behaviour. While Member States could offer certain types of incentives, such as tax rebates, few EU countries offered specific financial incentives[114] and they were insufficient. Also, Member States' action to boost paediatric medicines were largely unsuccessful[115].

The legislation respects Member States' exclusive competence in the provision of health services, including pricing and reimbursement policies and decisions as well as prescription of medicines

[112] The number of children below the age of 16 will have dropped by 14% between 2020 and 2070 (Eurostat 2019 projections).
[113] The Orphan Regulation is only based on the internal market provision, given that the Treaty of Lisbon that introduced additional competences in the field of health (i.e. Article 168 TFEU) did not exist at the time.
[114] Section 5.5 of the Joint Evaluation.
[115] Commission Staff Working Document – Proposal for a Regulation of the European Parliament and of the Council on medicinal products for paediatric use and amending Council Regulation (EC) No 1786/92, Directive 2001/83/EC and Regulation (EC) No 726/2004.

(Article 168(7) of the TFEU). Non-legislative actions at national level described in the Pharmaceutical Strategy for Europe will *complement* the legislative measures that will be proposed in this revision and in the revision of the general pharmaceutical legislation. They relate for instance to mutual learnings and best-practice exchanges in the area of pricing, payment and procurement policies.

3.3 Subsidiarity: Added value of EU action

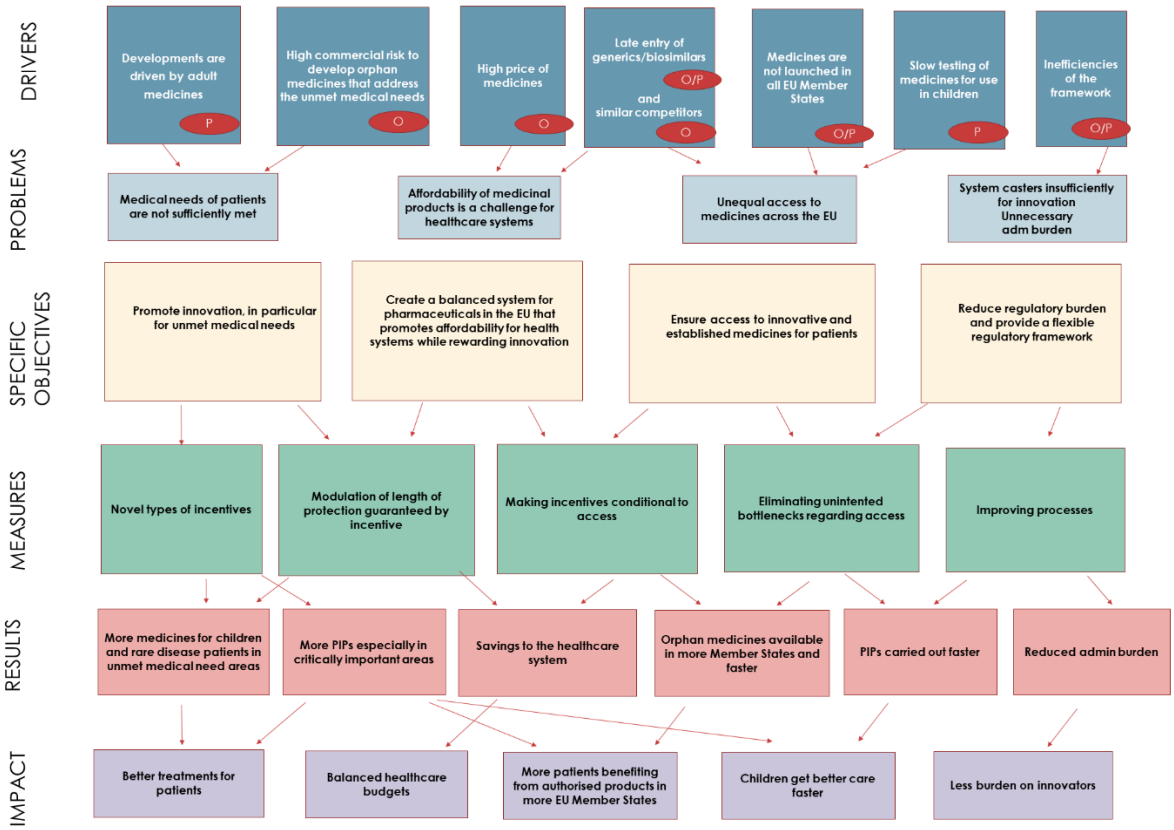
This initiative revises a system with recognised EU added value for the EU patients/citizens, pharmaceutical industry and medicines authorities leading to the authorisation of more medicines addressed to patients suffering from rare diseases and to children. It is expected to bring benefits by addressing unmet medical needs and contributing to reducing unequal patient access to medicines across the EU. At the same time, simplification and streamlining of processes are expected to reduce administrative burden for companies and hence improve the efficiency of the regulatory system. This revision can influence positively the competitive functioning of the market through the review of the incentives and other measures to facilitate entry of generic and biosimilar medicines and hence improve patient access and affordability.

4 OBJECTIVES: WHAT IS TO BE ACHIEVED?

4.1 General objectives

The intervention logic (Table 2) of this initiative builds on the one for the revision of the general legislation[116]. The overall objective of this initiative is to ensure a high level of health protection for all EU citizens and ensure that patients with rare diseases and children have access to high quality medicines and to safe and effective therapies to address their medical needs.

Table 2: Intervention logic



[116] Section 4.1 of the Staff Working Document – Impact assessment on the general pharmaceutical legislation.

4.2 Specific objectives

The revision of the legislations will aim to:

4.2.1 Promote innovation for rare diseases and for children in particular in areas of unmet medical need

Promoting innovation in all areas of rare and paediatric diseases is necessary, as there are still unmet medical needs. This is especially important for medical conditions where there are no treatment options, and for which the health burden is significant for patients suffering from rare diseases (*high* unmet medical needs) and for children. The revision should enable major biomedical research to advance and ensure a pipeline of innovative new medicines. It should also support pharmaceutical R&D and strengthen the competitiveness of the research-based EU pharmaceutical sector.

4.2.2 Create a more balanced system for pharmaceuticals in the EU that promotes affordability for health systems while rewarding innovation

The revision should promote affordability of medicines for health systems across the EU Affordability however should not be promoted at the expense of innovation, which also benefits patients. Thus, the underlying ambition is to create a balance where innovation is rewarded and faster market entry of generic and biosimilar medicines is facilitated, as a means to improve competition across the EU and drive down pharmaceutical costs for health systems.

4.2.3 Ensure timely patient access to orphan and paediatric medicines in all Member States

This objective aims to promote equal access to medicines for all EU citizens, including in smaller Member States. It can only partially be impacted by the pharmaceutical legislation[117]. After a medicine has been developed and authorised, patient access has two dimensions: (i) the equal access to/market entry of innovative medicines across the EU and (ii) continuous supply of all medicines. For this initiative, the focus is on the first dimension (the second being covered by the general pharmaceutical legislation)[118]. To ensure equal patient access across the EU, the aim is to provide a motivation to companies to reach an agreement with Member States more quickly and engage Member States in effective negotiations with the final aim to increase access for patients in more member States. Competition from generic and biosimilars will also serve patient access. Furthermore, a faster completion of paediatric clinical research would make products adapted for children more timely available.

4.2.4 Reduce the regulatory burden and provide a flexible regulatory framework

The revision should increase the attractiveness of the EU regulatory system through simplifying and regulatory requirements and reducing burden for industry and public authorities. The goal is to provide clarity on the regulatory pathways, reduce approval times and costs while maintaining high standards and robust assessment of the quality, safety, and efficacy of medicines. Leveraging digital technology and the use of electronic information could support this objective.

There are synergies between the various objectives, notably objectives 1 and 2 (they both cater for innovation purposes)[119] and between objectives 2 and 3 as more affordable medicines are

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[117] See also Section 2.1 of this SWD.

[118] As regards shortages and keeping products on the market, the aim is to enhance and harmonise notification requirements and obligations in the *general* pharmaceutical legislation to ensure appropriate and continued supply across Member States.

[119] Objectives 1 & 2 (unmet needs and patient access) can be related to Article 35 of the Charter of fundamental rights of the EU, which establishes the right to benefit from medical treatment under the conditions established by national laws

expected to become more accessible to more patients and health systems. On the other hand, some trade-offs between achieving patient access (objective 3) and rewarding innovation (objective 2) may be necessary, depending on market launch of innovative medicines[120]. Trade-offs are also inherent *within* objective 2, i.e. between rewarding innovative medicines and ensuring that medicines are affordable, which is often achieved by means of generic/biosimilar competition. A flexible regulatory framework with less regulatory burden (objective 4) will enable faster translation of innovation into authorised products in synergy with objectives 1+3.

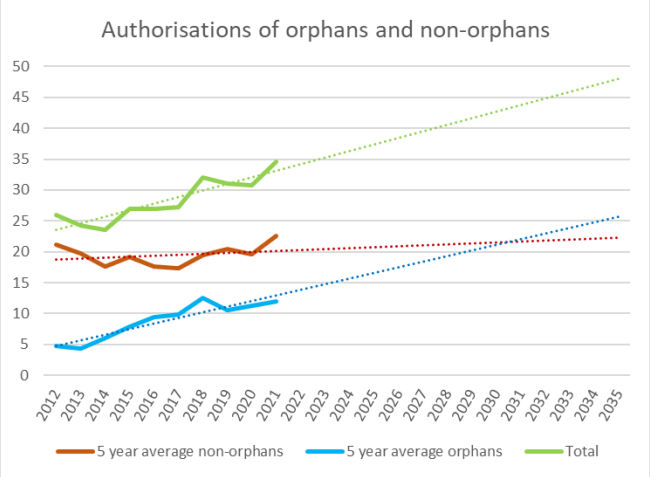
5 WHAT ARE THE AVAILABLE POLICY OPTIONS?

5.1 What is the baseline from which options are assessed?

The baseline is represented by the business-as-usual scenario, meaning the situation where no policy changes are made, with the current Paediatric and Orphan Regulations remaining in force. The revision of the general pharmaceutical legislation is factored into the baseline. The standard level of regulatory data protection will be reduced to 8 years, but medicines addressing unmet medical needs would receive an additional 1-year of protection, and medicines launched in all EU markets would get 1 additional year[121]. The changes due to the revision of the general pharmaceutical legislation are not expected to alter the number of new medicines (both orphan and non-orphan) on a scale that would influence the projections

To see how the **orphan medicines** landscape will evolve in the next 15 years (2020-2035) without any changes to the orphan regulation, a dynamic baseline has been developed against which the impacts of the policy options and common elements have been compared. Figure 1 below projects the number of orphan and non-orphan medicines based on historic EMA data, in line with the projection in the general pharma impact assessment. We expect the approval of 375 orphan medicines in the next 15 years, or an average of 25 orphans per year. Historic EMA data shows that out of the 190 authorised orphan medicines (2000-2020), 24% (or 46 products) targeted diseases that had no alternative treatment options. This is a good proxy for the share of high unmet medical needs, it has been assumed that a 20% share of orphan medicines developed/authorised up to 2035 will address HUMN, i.e. 5 products per year or 75 products in total.

Figure 1 – Number of authorisations for non-orphans and orphans



and practices and a high level of human health protection in the definition and implementation of all the Union's policies and activities.

[120] Often innovative products comes with a high cost which is not affordable by several Member States, reducing therefore the aces for patients.

[121] See also Section 6.1.1 of this SWD.

The increasing trend of orphan medicines will also raise further affordability issues. The average list price of new orphan medicines is expected to continue to increase, and generic competition will not be specifically fostered[122]. Regarding *patient access* to medicines, no major improvement would be expected. The amendment proposed for the length of regulatory protection for the revision of the pharmaceutical legislation would not impact the access for orphan products, as the 10 years market exclusivity protection would make it indifferent for orphan medicines whether they get 8+1 or 9+1 year's protection in the other legislation for launching in all member states. Moreover, the effective period of market exclusivity would continue to be longer than 10 years, as generics/biosimilar can only file after expiry not enter the market thereby delaying generic entry.

For **medicines for children**, EMA data shows that in the last 5 years 60% of new applications were obliged to carry out PIPs and 40% were exempted by a waiver. We expect a similar ratio for the coming years among newly authorised medicines. Therefore, out of the 675[123] new medicines expected to be authorised in the next 15 years, it has been assumed that **405** would have been obliged to carry out paediatric studies. This is not however equivalent to the number of new medicines available to children, as studies may conclude that the medicine is inappropriate for paediatric use. The current procedure for agreeing a PIP, would continue to allow products with the potential to address important unmet medical needs for children (e.g. certain anti-cancer medicines) to escape the obligation[124]. Moreover, more and more innovative products may struggle with the current requirement to present a complete clinical development plan at very early stage of development as such, risking to delay their development and increasing the administrative costs for the PIP procedure. Beyond the obligations, the paediatric regulation rewards timely completion of PIP with a 6-month SPC extension. Some medicines will complete a PIP, but will not benefit from the reward if they do not have an SPC protection (i.e. 50% of new medicines) or if the completion is so late that they cannot claim anymore the extension[125]. Out of the 45 new medicines, 60% will have a PIP obligation and of them 35-40% will be able to redeem the incentive: we expect 10 new SPC extensions annually. Regarding the budgetary impact of the reward, there will be a tangible increase in the number of SPC extensions awarded going from the current four per year[126] on average to ten. The SPC extension will apply to all sales of the product, not just those intended for use in children. The value of the reward and consequently the additional cost for health payers depend on the revenues generated by the rewarded medicine. While the evaluation has shown that on average the SPC has provided a fair reward for conducting PIPs, there are some blockbuster medicines[127] for which a six-month extension means hundreds of millions extra revenue and others for which it brings no extra revenue (those that rely on RP or patent as last line of protection). As for timely access to paediatric use of new adult medicines, the baseline does not offer any improvement. Currently, 86% of PIPs include deferrals, meaning that the completion of the PIPs can be delayed to after the market authorisation for most new medicines. Analyses on the basis of data provided by the Agency demonstrated that the average expected PIP duration was 9.18 years and more than 7 years for around the 70 % of the PIPs.

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[122] See also Section 2.1 of this SWD.

[123] Referring to the projections of the general pharma impact assessment, assuming 40-50 new medicines yearly on average for the next 15 years.

[124] See also Section 2.1 of this SWD.

[125] The extension must be claimed 2 years before SPC expiry the latest.

[126] Currently on average 4 extensions are utilised per year but taking into account the timing necessary to complete a PIP, an increased number of PIPs are foreseen to be concluded in the coming years.

[127] We have noted that out of 12 blockbuster medicines (those that have a revenue of €1 billion per year in the EU market) in a basket of products analysed, 8 had a paediatric extension; see also *F. Schmidt*, Beyond protecting economic interest, SPCs as a tool to support public health goals, EPLR 2018, p. 63.

5.2 Description of the policy options

The different policy options vary as to the incentives or rewards to which orphan and paediatric products would be entitled to. In addition, the revision will include a series of common elements that are present in all the options. Each policy option aims to address all the objectives and all the problems identified. The options are in line with the measures considered in the revision of the general pharmaceutical legislation. The situation in other jurisdictions (notably the US and Japan) has been taken into account (see sections 1.3.3 and Annex 8). A tabular description of the options and a further description of the various elements is provided in Annex 5.

5.2.1 Medicines for rare diseases

The following policy options have been assessed.

- **Option A:** keeps the 10 years of market exclusivity and adds - as an additional incentive - a transferable regulatory protection voucher for products addressing HUMN of patients. Such a voucher allows for a one-year extension in the length of regulatory protection and can be sold to another company and used for a product in that company's portfolio (more details in Annex 4 section 5).
- **Option B:** abolishes the current market exclusivity of 10 years for all orphan medicines.
- **Option C:** provides for a variable duration[128] of market exclusivity of 10, 9 and 5 years, based on the type of orphan medicine i.e. for HUMN, new active substances and well-established use applications, respectively. A 'bonus' market exclusivity extension of 1 year can be granted, based on patient accessibility within 2 years of authorisation in all relevant Member States (that has patients), but only for HUMN products and new active substances.

  Similarly to the concept of the revision of the general pharma legislation, companies could still receive the market launch incentive if, due to reasons beyond their control, the market launch is delayed or missed (e.g. the Member State doesn't wish to be supplied at that particular moment or doesn't have the specialised infrastructure, e.g. in case of ATMPs). The specific situation of **SMEs and not-for-profit entities** and their capacity to engage in multiple parallel pricing negotiations will be taken into account by allowing a 1-year longer period to comply with the market launch conditions.

Regulatory data protection[129] - as provided by the general pharmaceutical legislation - will also apply to orphan medicines.

Elements common to all policy options

- **Stimulate innovation** (to improve research and development especially in areas of (high) unmet medical needs – **objective 1**):
  - Criteria to identify products addressing HUMN will be set in the orphan legislation[130]. Such products would address areas where no treatment is available. The definition of such criteria – in combination with the incentives geared towards medicines addressing HUMN – aim to support the development of these medicines.
  - Products addressing HUMN will be **entitled to increased scientific support by the Agency**[131]. The enhanced interaction with developers of promising medicines for

[128] As regards the international outlook, important comparators like the US and Japan provide 7 and 10 years of market exclusivity, respectively. The tested durations were selected to ensure coherency with the selected length of the regulatory protection under the proposed preferred option of the revision of the general pharmaceutical legislation.
[129] See also Section 1.2.3. of this SWD.
[130] See Annex 9 for the criteria considered.
[131] E.g., scientific advice, PRIME, rolling review.

HUMN will optimise their development plans and speed up evaluation so these medicines can reach patients earlier.

- **Faster generic/biosimilar competition** (to improve affordability and patient access – **(objectives 2&3**):
    - Generics/biosimilars can enter the market **at day-1** of the expiry of the exclusivity period[132] by allowing the filing of an application prior to expiry. This will align the regime for generics with the one of the general pharmaceutical legislation.
    - Reduction of **consecutive periods of market exclusivity** for new indications of the same orphan medicine by introducing them under the same "Global Marketing Authorisation" (GMA). To ensure that both new indications are developed and that possible multiple and consecutive extensions of a full market exclusivity duration are reduced (the latter with negative consequences for affordability), the second and third indication authorised will be rewarded with a 1-year extension each of the overall market exclusivity period[133]. This will limit consecutive durations of the market exclusivity and is therefore especially intended to support affordability, as it will lead to shorter durations of market exclusivity and faster generic/biosimilar competition.
    - The market exclusivity **granted to a second generation product that is similar** to the first generation product will not be applied in respect of generic products of the first reference product for which the market exclusivity expired[134]**.** This will avoid evergreening[135] [136].
    - **Encourage companies that lose the commercial interest in an orphan medicine to offer it for transfer to another company** rather than withdrawing it. This is intended to improve patient access as more products will remain on the market[137].
    - **The duration of the orphan designation** (assigned early in the development of a product and prior to obtaining a marketing authorisation) will be **capped** for newly designated orphan medicinal products at 7 years (there is no limit today) to stimulate timely product development[138]. These measures are intended to ensure an increase in availability and timely access of patients.
- **Reduce the regulatory burden and provide a flexible regulatory framework (objective 4):**
    - **Provide for the possibility to adapt the current definition of an orphan condition** to ensure that the legislation is 'fit' to embrace technological and scientific

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[132] Currently, a marketing authorisation dossier can only be submitted at the end of the marketing authorisation period.

[133] This additional market exclusivity would apply to the product itself, not just to the specific indication. This implies a maximum of 12 years of total market exclusivity to various orphan indications related to one product.

[134] Section 5.2.3 of the Joint Evaluation.

[135] Second, independent periods of market exclusivity were contested in Case T-140/12. "Evergreening" strategies extend the effective protection period and thus allow pharmaceutical companies to maintain a market share after their protections expire by introducing "follow-on drugs" - those with slight changes made to them after expired protections that would normally allow generic competitors to enter the market.

[136] It will therefore address an unintended consequence of the current orphan legislation, namely that currently it is possible for an originator to obtain market exclusivity for a second generation product that is *similar* to the first generation product (thereby preventing swift generic/biosimilar competition).

[137] The Joint Evaluation (Section 5.1) found that 11 authorised orphan medicinal products were withdrawn (between 2000 and 2017). If the companies of these products can be encouraged to offer it for transfer, this would improve overall timely authorisation of orphan medicinal products and patient access across Member States. A transfer of the marketing authorisation can be done under Regulation (EC) No 2141/96 free of charge.

[138] The Joint Evaluation (Section 6) concluded that this transformation from concept to an authorised orphan medicine remains slow. Capping the orphan designation could lead to expiry of some of those designations, but may also encourage companies to quicker advance the authorisation process. In view of the average time of 5 years between designation and authorisation, a 'cap' of 7 years provides a buffer factoring in potential longer development timelines in individual cases; such cap should lead to a few extra products being developed.

advances[139]. This is intended to support the development of products in HUMN areas (objective 1) and to cater for efficient procedures for designation and authorisation.
    - **The orphan designation criterion[140] on the basis of return on investment** will be abolished, since it has never been used[141].
    - **Responsibility for adopting decisions on 'orphan designations'** will be transferred from the Commission to the Agency. These measures are intended to provide more effective and efficient procedures.

5.2.2 Medicines for children

The following policy options have been assessed. They all include the common elements and differentiate by changes to the system of rewards provided to developers of medicines.

- **Option A**: the 6 months SPC extension is kept for all medicinal products. Furthermore, an extra reward benefiting products addressing UMN of children is added (criteria to identify these products will be defined in legislation). This will consist of: either 12 extra months of SPC extension; or a regulatory protection voucher (duration 1 year) which could be transferred to another product (possibly of another company) against payment, allowing the receiving product to benefit from extended data protection (+ 1 year). This would aim to boost the development of products of addressing unmet medical needs of children.
- **Option B**: the reward for the completion of a PIP is abolished. Developers of every new medicine would continue to be obliged to agree with the Agency and conduct a PIP but the extra costs incurred would not be rewarded. As today the SPC extension comes at a cost to health systems, with impact also on accessibility for patients, the elimination of the reward would contribute to ensure an early entry of generic products and therefore reduce the financial impact on health systems and in parallel facilitate access for more patients.
- **Option C**: The 6 months SPC extension remains the main reward for the PIP completion.

Elements common to all policy options:

- Criteria to identify products which have the potential to address **unmet medical need of children** will be defined in the general pharmaceutical legislation[142]. Products which respond to these criteria will be entitled to **increased scientific support[143] by the Agency** in the early phases of development (**objective 1**).
- The **procedure for setting out a PIP** will be **streamlined and simplified** to better reflect how medicines are developed. The new system will allow for a dynamic plan on the basis of the clinical results obtained (evolutionary PIP). This allows to better accommodate innovation (**objective 1**), a quicker completion of the PIP and faster authorisation (**objective 3**) reducing administrative burden for companies also for PUMA products (**objective 4**).

[139] If need be, delegated acts to facilitate the adaptation of the orphan condition concept to scientific and technological progress can be foreseen, for instance to avoid that the concept of personalised medicine would make every medicine an orphan. Current Guidelines can continue to ensure that the regulatory framework is not improperly used leading to orphan designations for artificial subsets of common diseases.
[140] The designation criterion of insufficient return on investment (Article 3 (1a) of the current Orphan Regulation).
[141] Section 5.1 of the Joint Evaluation.
[142] See also Annex 9 for the criteria to be considered.
[143] The scientific support by the Agency provides targeted, product and development-stage specific advice from experts to increase likelihood for authorisation. This is different to the financial support in form of grants potentially provided by Horizon Europe.

- **The length of deferrals** will be capped to 5 years[144], so that products reach children quicker than today (**objective 3**).
- **Mechanism of action of a product**. Products which, on the basis of scientific evidence on the mechanism of action, could be effective against a different disease in children[145], have to perform a PIP. This will favour the development of products addressing unmet needs of children (**objective 1**). A similar obligation on the basis of the mechanism of action already exists in the US[146] and would thus align the legal frameworks
- **Abolishing the market exclusivity extension** for completing PIPs would allow predictability for generic products and faster entry of generics **(objective 2 and 3).**

5.3 Options discarded at an early stage

For *paediatric* medicines, the possibility to create lists of unmet needs for children has been discarded. Such possibility has received limited support from all stakeholders. Furthermore, an inventory of therapeutic needs for children is already foreseen by the current Regulation. Such inventory has not be useful to steer development of new products and has been challenging to be kept updated by the Agency. While academics and patients mentioned the need to have multistakeholders consultation to discuss about prioritisation in the development of medicines, such activities are already taken place under the EMA/Commission action plan and do not need any legal revision to continue[147]. There have not been any options discarded for orphan medicinal products.

6 WHAT ARE THE IMPACTS OF THE POLICY OPTIONS?

This section includes an analysis of the main economic and social impacts of the policy measures in the different policy options. The analysis focuses first on the impacts of measures concerning orphan medicines, then paediatric medicines. Finally, it analyses some impacts which are relevant for both. The impacts of the options were assessed in an iterative process, taking into consideration (public and targeted) consultations with stakeholders, literature review, and quantitative analysis where possible. Details of the methodology are available in Annex 4, and a summary of stakeholders' views in Annex 2.

6.1 Medicines for rare diseases

The economic impacts of the policy options on the main stakeholders (industry, public authorities, patients) has been assessed and quantified by focusing on: a) assessing the potential effects of changes to the extension of the Market Exclusivity under the various options (including the introduction of a novel reward under option A); b) assessing the impact of the common elements. Other economic impacts have been considered and they are detailed here below by stakeholder group

6.1.1 Economic impacts of the policy options

Health systems/payers derive benefits in the form of savings from avoided hospitalisation and avoided outpatient treatments due to the number of (HUMN) products authorised for use in patients

[144] The length of the derogation has been assessed taking into account the average length of PIP with and without deferrals. More information can be found in Annex 4, section 7.
[145] During the consultation activities this was supported by academia and civil society respondents. Industry was initially opposing this measure, their position has however evolved and they are also now supporting it.
[146] See Race The Children Act and https://www.kidsvcancer.org/race-for-children-act/. The Agency is collaborating with FDA in setting up non exhaustive lists of known mechanism of actions. However, as in the US it will be the responsibility of each company to indicate, when applying for a waiver the non-existence of relevant mechanism of action for their products.
[147] Joint action plan to support the development of medicines for children in Europe.

suffering from a rare disease. Costs mainly elate to the extra year of market exclusivity for HUMN and access, and the subsequent delay in entry of generics/biosimilars[148].

Patients' costs and benefits derive from delayed/faster access to the products developed, in particular in areas of HUMN. Other impact on patients are assessed in the social impact section.

Originators will benefit from simplified regulatory procedures and more gross profit from the sales of new (HUMN) orphan medicines. Costs mainly relate to gross profit loss due to the access incentive conditionality and faster entry of generics/biosimilars after the expiry of the market exclusivity. In particular, SMEs will benefit considerably from simplified procedures and scientific support by the Agency. The **generic industry** will also benefit from simplified procedures and more gross profit due to a predictable and earlier market entry when originators do not comply with the market launch conditionality. Costs mainly relate to longer protected sales of (HUMN) originators' orphan medicines.

Which medicines are affected by changes in market exclusivity?

Market exclusivity (ME) is the main feature of the Orphan Regulation, providing a form of protection from generic/biosimilar competition with distinctive characteristics[149].The main variable of the different policy options is the length and conditions of this incentive. However, ME does not play in isolation: the regulatory data and market protection (RDP) granted by the general pharmaceutical legislation and other IP incentives, notably patents and SPCs, also protect against generic competition. While the current ME (10 years with a maximum of 12 years if a paediatric research and development programme is completed[150]) and RDP protection (10 years) start from marketing authorisation, the patent (20 years) and SPC (5-year extension of primary patent - maximum 15 years from marketing authorisation) is counted from patent filing, many years before market authorisation. Depending on the time elapsed between patent filing and authorisation, and whether the medicine is orphan or not, one of these four protections will last for the longest period[151]. Table 3 presents orphan medicines that lose their last protection between 2016 and 2024, based on the type and length of last layer of protection to expire.

Table 3: Length and type of protection of orphan medicines

	Years of protection after market authorisation											
Last line of protection	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19+**	**Grand Total (years)**	**Avg peak annual sales[152]**
Market Exclusivity	10		4								**14**	€ 41.4 m
SPC			2			4	2				**8**	€ 475.8 m
Patent						1	1	1	1		**4**	€ 248.0 m
Grand Total	10		6			5	3	1	1		**26**	€ 206.8 m

Source: IQVIA

[148] The *societal* costs of a disease are considered to be wider than those borne by healthcare systems. The non-healthcare costs of a disease are the use of social services; the costs of involvement of carers; and productivity losses resulting from unplanned absences from work or early retirement by patients (or carers). However, any wider societal impact could not be established at the level of the Orphan Regulation. See also Section 5.2 of the Joint Evaluation.

[149] For a full description of market exclusivity see Section 1.2.2.

[150] See Section 1.2.4 of this SWD.

[151] Copenhagen Economics - Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe (2018)

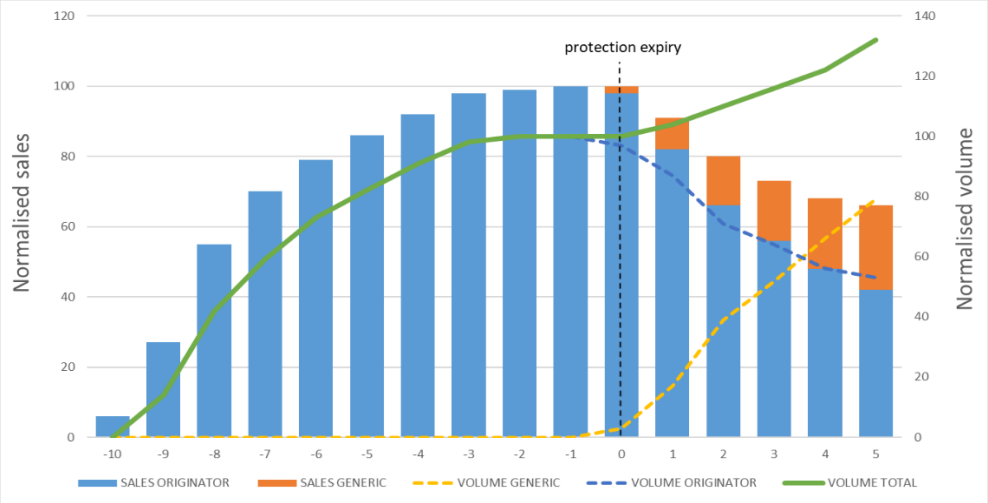
[152] Annual revenue of the medicine in its best-selling year over its lifetime (usually the last year before protection expiry).

ME is the last layer of protection for about half of the medicines (14 of 26) offering either 10 or 12 years of protection. For the remaining other half of medicines, SPC and patent are the last layer of protection, in most cases 15 years or more. These medicines generate much higher revenues on average than the ME-reliant medicines. **Thus, changes to market exclusivity are expected to affect around 50% of orphan medicines in practice with far lower revenues than the average.** Thus, out of the 25 orphan medicines that we expect to be authorised annually 15 years from now, it is expected that half, i.e. 12-13, will be reliant on market exclusivity as last line of protection. Out of these, around 20% (or 2-3 products) will address HUMN (see also Section 5.1).

How market exclusivity protection generates value/cost for stakeholders

To calculate benefits and costs deriving from market exclusivity, the analysis relied on the conceptual model presented in the revision of the general pharmaceutical legislation impact assessment, which follows the lifecycle of a representative innovative medicine (Annex 7, sections 3 and 3.b)). This analogue in Figure 2 below is extracted from analysing historical sales data of innovative medicines and their generic competitors before and after protection expiry[153]. During market protection period, innovators can enjoy high monopoly revenues. Once the protection expires, the generic medicines enter the market with a lower price, carve out a growing market share and force the originator to offer discounts[154]. The volume of generic medicines steeply increases, partly because some users substitute the originator medicine with generics and partly because the total volume rises with increased affordability. For health systems, the price drop following generic competition means cost savings. Extending the protection allow innovators to seek longer monopoly rents, but it delays cost savings and broader access for the public and delays revenues for generic companies. Decreasing protection has the exact reverse effect.

Figure 2: Normalised sales and volumes of originator and generic products



The analogue allows to measure economic impact of the change for the different stakeholders, however the unit of measurement is different for the various stakeholders:

- For **health payers** we measure the impact of changes by the change in the **cost of medicines**, which can be directly deducted from the total sales of originator and generic medicines in the IQVIA data.

[153] Description of the methodology and analogues is further elaborated in Annex 4 (sub-sections 1.1, 1.2 and 1.3) of this SWD.

[154] The evaluation of the generic pharma legislation found that originator products can maintain a 30% premium over their generic competitors.

- For **patients**, we measure the impact of change by the change in the **volume of medicines**. The more/less the volume, the more/less patients could benefit from therapy, either using the originator or the generic product. We present the volume change in a monetised form, by showing the monetary value of the additional or lost volume of medicines. In the analysis we refer to this as *"Δ of patients treated (monetised)"*.
- For **originator** and **generic industry,** the key measure of impact is **the gross profit** that they can realise from their business operations. Gross profits are calculated by subtracting estimated manufacturing and distribution costs from revenues according to the methodology set out in Annex 4.

We have the tools to monetise the direct economic impacts of the incentives. However, the incentives serve a purpose, e.g. they stimulate development of therapies for unmet medical needs, enable faster and broader patient access. **Monetising these societal benefits has practical and ethical challenges**: there is a large variation among medicines' value, influenced by the patient population, the nature and severity of disease, etc. Moreover, monetising the social benefits requires putting a monetary value on patients' life and health, as well as on the physical and emotional burden of their families and carers. We thus have chosen not to monetise these impacts, rather quantify them as much as possible, explain them in the text, and highlight them in the summary cost-benefit tables.

Option A – keep market exclusivity unchanged and add a novel incentive

Retaining the 10 years market exclusivity does not have an economic impact on the orphans compared to the baseline. However, the 10-year protection, granted regardless whether the product is launched in all EU countries or not, would neutralise the access incentive of the general pharma legislation for what concerns orphan medicines (see Table 4 below).

Table 4: Length of regulatory protection and market exclusivity in Option A

Option A	Regulatory protection	Market exclusivity	Last layer of protection	ME added value
Orphan medicines launched in all EU	9 (8+1)	10	ME	+1 year
Orphans NOT launched in all EU	8	10	ME	+ 2 years

.

Option A also introduces **a novel incentive** for products addressing HUMN, namely *transferrable exclusivity vouchers*. Such a voucher could be used to extend the protection of another medicine of the developer, or the developer can sell the voucher to another company (transferable), which then can use it for a medicine in its own portfolio, likely a blockbuster.

The impact assessment on the revision of the *general* pharmaceutical legislation[155] discusses the case for using such an incentive for the development of novel antimicrobials. It has been argued, in particular by the pharmaceutical industry[156], that orphan medicinal products are also a good candidate for a novel incentive, like the vouchers, given that they serve small populations and the profits that they promise to generate may not direct sufficient resources to their development.

However, rare disease medicines have become more important revenue generators[157] and, moreover, a transferable exclusivity voucher would be ill-suited as an incentive to promote investment in HUMN products for rare diseases. This is because the number of vouchers would inevitably become

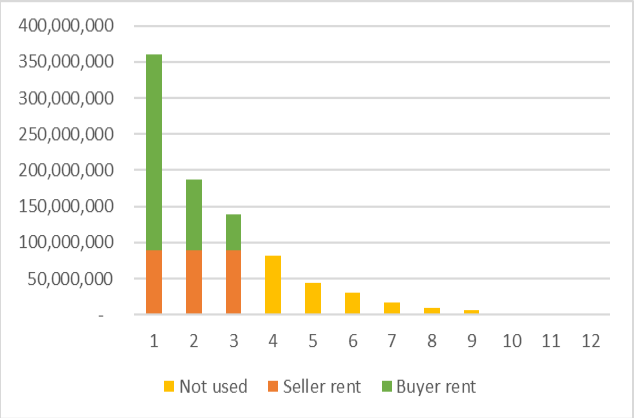
[155] Staff Working Document – Impact assessment on the general pharmaceutical legislation (Section 6).
[156] See also Annex 2: stakeholder consultation (synopsis report).
[157] As explained above under 'baseline scenario' in Section 6 of this SWD.

too high (considerably higher than in the case of antimicrobials) and their power as an incentive would thereby be severely undermined. This would also nullify the value of vouchers as an incentive for novel antimicrobials. This consideration applies *a fortiori* to medicines addressing an unmet need for children, given that the number would be even higher and the case for an inability of these products to generate revenue is even weaker.

A voucher operates as an incentive, because it confers a rent on the voucher holder. An economic rent is a revenue that accrues on the basis of ownership of a limited asset or resource without requiring commensurate risk or effort[158]. The value of such a rent-generating asset resides in its rarity. When vouchers becomes less rare, the rent associated with all vouchers is diminished. The analysis below, which is developed further in Annex 4, uses real world data to estimate the rate at this occurs, i.e. the nature of the inverse relationship between the size of the rent and the number of values issued.

It is estimated that there will be 3-6 HUMN medicines for rare diseases per year and this will entail competition among voucher sellers that will ensure that by far the larger share of the rent associated with the voucher accrues to the voucher *buyer*. This rent, which comes at a high cost for payers, is a by-product of the rewards for pharmaceutical companies with the highest revenue-generating medicines and does not contribute to the intended incentive[159]. **Figure 3** models two scenarios, one with three HUMN medicines per year and one with six and demonstrates how the benefits of the incentive are shared among the voucher buyers and sellers in the two cases. The green and orange bars are the RDP-protected products from the annual cohort for which a voucher is bought, with the value of the voucher split between buyer rent and seller rent. The yellow bars are the RDP-protected products for which no voucher is bought (Annex 7, section 5).

Figure 3 – the seller and buyer share of voucher rent varies with the number of vouchers



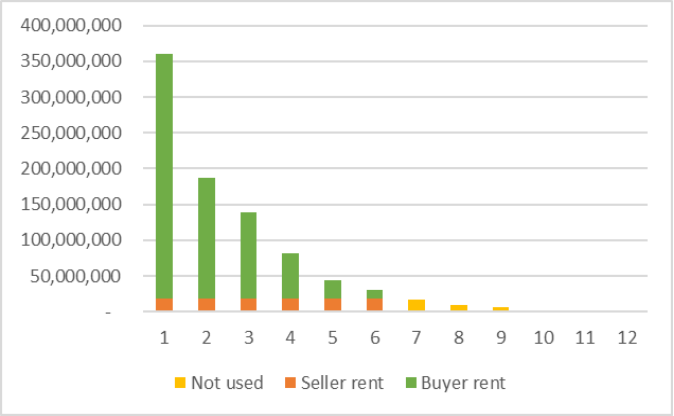


Table 5 – economic impact of the voucher	Systemic change (5 HUMN/year)
Gross profit of HUMN developer	**+€151m**
Gross profit of voucher buyers	+€576m

[158] Economic rents | UCL Institute for Innovation and Public Purpose - UCL – University College London

[159] With the exception of the small minority of products that enjoy an additional year of protection thanks to an additional indication under the current regime, these products were authorised 10 years before their protection expired, so the sample comprises those medicines that were authorised in the period 2004-2014.

Generics gross profit	-€122m
Cost to public payer	**+€639m**
Δ of patients treated (monetised)	--€355m
Patients + payer gain/loss	**-€994m**

With three vouchers issued a year, the seller's rent is already less than the buyer's share at 39%. With six, it is only 13%, with the remaining 87% captured by companies that are not the intended beneficiaries of the scheme.

Table 5 summarises the economic impacts of the incentive on the different stakeholders, if 5 HUMN medicines for rare diseases per year are awarded (in line with the assumptions presented in the baseline). The direct cost to the public payer is around €639m, and if we take into account unserved patients due to retained high prices, **a billion euros loss to the public** is expected, and only a small fraction of it (€151m) would benefit the 5 developers, €30m each. It is estimated that the incentive would induce around 5 more HUMN addressing orphan medicines over 15 years.

Option B – no market exclusivity

Option B proposes the complete **elimination of market exclusivity** in an attempt to address affordability and the high cost of orphan medicines. However, the orphan medicines would not lose 10 years of protection, because the revised regime for regulatory data protection[160] also provides an 8- or 9-year[161] protection for all medicines, including orphans (Table 6).

Table 6: Length of regulatory protection and market exclusivity in Option B

	Regulatory protection	Market exclusivity	Last layer of protection	Change to baseline
Orphan medicines launched in all EU	9 (8+1)	0	RP	-1 year
Orphans NOT launched in all EU	8	0	RP	-2 years

Option B would result in a 1-year protection loss for orphan medicines that are launched in all EU countries and a 2-year loss for those that are not, because of the revised regulatory protection in general pharma. In accordance with baseline projections, we expect 10 orphan medicines annually where the market exclusivity is the last layer of protection of these, we expect that 4 would comply with market launch in all Member States and 6 would not.

With these input variables our model in Annex 4 (section 3.c.i) leads to the following results per stakeholder (see Table 7).

Table 7 – economic impact of no market exclusivity in combination with changes of regulatory protection

	Product level change 1 year loss	Product level change 2 years loss	Systemic change (4 all-EU launch, 6 not all-EU)
Originator gross profit	**-€47m**	**-€94m**	**-€751m**
Generic gross profit	**+€6m**	**+€13m**	**+€101m**
Cost to public payer	-€27m	-€54m	-€430m
Δ of patients treated (monetised)	+€21m	+€35m	+€295m
Patients + payer monetised gain/loss	**+€48m**	**+€89m**	**+€725m**

[160] This change will derive from the revision of the general pharmaceutical legislation.
[161] If the market launch conditionality is fulfilled.

Option B would generate an annual €430m savings to public payers, and with the additional patients served thanks to earlier price competition, the public saving amounts to €725m a year (over the annual €40-50bn that the EU spends on orphan medicines). Apart from supporting affordability, this option also contributes to improving access by allowing the incentive introduced in the general pharmaceutical legislation to affect orphan medicines.

For developers of orphan medicines, the direct impact of abolishing the incentive would be €751m in lost profits. This impact would be amplified by the message transmitted to patients, researchers, companies and investors active in the rare disease area. Divestments and shifting research priorities would likely withdraw resources from orphan medicines development and would be negatively perceived by all stakeholders.

Option C – modulation of market exclusivity to match regulatory protection[162].

Table 8: Length of regulatory protection and market exclusivity in Option C

	Regulatory protection	Market exclusivity	Last layer of protection	Change to baseline
Orphan medicines launched in all EU	9 (8+1)	10	ME	0 year
HUMN orphans launched in all EU	9 (8+1)	11	ME	+1 year
Orphans NOT in all EU	8	9	ME	-1 year
HUMN orphans NOT in all EU	8	10	ME	0 year
Well-established use orphans	0	5	ME	-5 years

+1 year for HUMN addressing orphan medicines

To demonstrate the impacts of **1 year protection extension for medicines addressing HUMN**, we again use the analogue elaborated in Annex 4 (section 3.d). In accordance with baseline projections, we expect that from the 10 orphan medicines annually where the market exclusivity is the last layer of protection, 20% or two products **would address HUMN** and therefore be eligible for the extra year.

Table 9 – Impact of change of +1 year market exclusivity protection

	Product level change	% change	Systemic change (2 medicines)
Originator gross profit	**+€47m**	**+7.7%**	**+€94m**
Generic gross profit	-€6.5m	-28%	-€13m
Cost to public payer	**+€27m**	**-2.9%**	**+€54m**
Δ of patients treated (monetised)	**-€14m**	-2.4%	**-€28m**
Patients + payer monetised gain/loss	**-€41m**	**-4.3%**	**-€82m**

[162] It follows the general pharma legislation by offering a lower, 9 years market exclusivity as a default, which can be extended by 1 year if the medicine is launched in all EU markets. Furthermore, products addressing HUMN would be granted a market exclusivity extension of 1 year (i.e. 10 years as a default for HUMN products).

We estimate that **an average orphan medicine addressing HUMN** and relying on market exclusivity as last line of protection **will be able to generate €47m more profit** (or 7.7% more than in baseline). Such medicines will become more attractive commercially for developers, and their proportion among the newly authorised medicines would increase. We estimate that instead of the 75 projected HUMN addressing orphan medicines in the dynamic baseline (Section 5.1), there would be 80-85 HUMN products authorised in the next 15 years.

The cost of a +1 year protection for HUMN protection would be shared among generic industry, health payers and patients. With 2 of such incentives annually, the generic industry would lose €38m in revenues a year, which translates into €13m decrease in gross profits. The **health payers would need to pay €54m more on an annual basis**. The model also accounts for the patients that would not be served due to the higher prices that result from extended protection. Accounting for that effect too, the **cost for the public would rise by €82m annually**. In exchange for this public cost, the HUMN incentive would directly reward investment in HUMN R&D and likely would have a spill-over effect by sending a signal about the importance of HUMN orphan medicines[163].

Access conditionality

Option C offers the same market exclusivity period for standard orphan medicines as the baseline, 10 years, but only if the medicine is launched in all EU markets within 2 years of authorisation. If not launched in all markets, the protection period is 9 years. This aims to motivate companies to launch in all EU member states, and not to leave out small markets, which are not attractive enough commercially. Similarly to the general pharma revision, it is expected that some medicines will not comply with the access incentive conditions. Given the lower level of baseline compliance with the proposed conditionality of orphan medicines reliant on ME compared to non-orphan medicines reliant on RP, the gap to be bridged will be larger. The assumption is therefore made that 40% of orphan medicines will comply (for non-orphans it is 50%[164]), and 60% will not. Thus, of the 10 orphan medicines expected to have ME as last line of protection, we expect that 4 would comply with market launch in all Member States (and 6 not).

If a standard orphan medicine is **launched in all EU member-states**, the reward will have the same economic impact as in the baseline, with the 10-year market exclusivity protection.

No distinction is made here between HUMN and non-HUMN ME-reliant orphan medicines (the total of 10 includes both), since in either case, the length of protection will be increased by one year if the access conditionality is met as compared with those that do not comply. The table below therefore accounts for both cases, using the model from Annex 4 (section 3.c.ii and section 6):

	Product level change	% change	Systemic change (6 medicines)
Originator gross profit	**-€47m**	**-7.7%**	**-€282m**
Generic gross profit	+€6m	+28%	+€38m
Cost to public payer	**-€27m**	**+2.9%**	**-€162m**
Δ of patients treated (monetised)	+€21m	+2.4%	+€126m
Patients + payer monetised gain/loss	+€48m	+5.0%	**+€288m**

[163] It is expected that national and EU-level research funding programmes would follow suit, and channel resources specifically to HUMN addressing innovation. National pricing and reimbursement systems could also differentiate the HUMN addressing orphans, making marketing conditions more beneficial to them. The same spill-over affects across the ecosystem were visible following the adoption of the orphan regulation, bearing its fruits 10-20 years later.
[164] General pharma IA SWD, Section 8.1.

Table 10 – Impact of change of -1 year market exclusivity in case of non-launch in all MS

For the public payer/patient this instrument is a win-win, if medicines comply, timely access across the EU will increase, and if not, the protection period decreases, lowering cost for society by 48m. The decreased protection translates to 47m lower gross profit per medicine, or 282m for the whole innovative industry and to 38m higher profit for the generic industry. These impacts show only the direct economic impact of the *incentive*. However, there is an expected and non-monetised **positive societal impact**, in the form of **faster, increased and more equitable access** across the EU.

Well-established medicines

Option C also replaces the current additional 10 years with 5 years of market exclusivity protection for **well-established use medicines**, those that have already lost their other protections and for which generic versions exist. Products authorised through this 'route' have attracted substantial scrutiny because of cases in which producers substantially increased the price once the market exclusivity was granted for the newly-authorised medicine that was previously available to patients at a far lower price as a magistral formula or in the form of hospital preparation[165]. The shorter duration still rewards the effort to obtain a marketing authorisation and comply with the high safety and quality standards of an authorised product but reflects that these established medicines have encountered less development risks. It also addresses to a certain extent prolonged price hikes.

The adoption the orphan regulation offered the opportunity for companies to "orphanise" old medicines and many seized the opportunity. By now such low-hanging fruits are harvested and we expect only a few (2-3) well-established use market exclusivities granted per year in the future. Given the low frequency and little value of protection (protection only in a rare indication with co-existing generics), the economic impacts are insignificant in comparison to the other measures.

Stakeholder views

No stakeholder group asked to abolish the market exclusivity, which is the current main incentive (market exclusivity) that fosters developments in the area of orphan medicinal products. It has been suggested that such measure would send a negative signal to patients, researchers and developers and would undermine several efforts the EU does in research and innovation (Horizon Europe) and for rare disease patients (European Reference Networks).

Most stakeholder groups agreed that a revision of the current incentive system is needed (although pharmaceutical industry wanted more) by creating a connection between incentives and obligations. A *variable* duration of the market exclusivity (**Option C**) would answer respondents' concerns that the current 'one-size-fits-all' incentive framework is not sustainable for national healthcare systems. It will also better take into account the focus on product development for greatest patient needs and the costs of development for the product. Health payers and public authorities[166] emphasised that

[165] Leadiant® gained an orphan designation in 2014 and a marketing authorisation in 2017 for the treatment of cerebrotendinous xanthomatosism. Before the market entry of Leadiant®, patients with cerebrotendinous xanthomatosis were treated with off-label drugs with the same active ingredient, at a very low cost per patient. From 2017 towards the end of 2020, the average price of Leadiant® suddenly excessively increased. National competition authorities in the Netherlands, Italy and Spain undertook proceedings about Leadiant's excessive price increase and found it disproportionate as the orphan medicine was not 'innovative' and not requiring substantial investments in the development. See also: ACM imposes fine on drug manufacturer Leadiant for CDCA's excessive price | ACM.nl

[166] Public authorities favour a market exclusivity with a shorter initial duration in cases where the development effort is simpler as it has been based on known off-label treatments. This would be taken on-board under Option C, allowing for earlier market entry of (similar) competitor products in case of orphan medicines that are authorised on the basis of bibliographical data (well-established use) or not falling in the category of HUMN.

rewards and incentives should be *differentiated* and highest incentives should be concentrated mainly on areas where no treatment options are available.

Impacts of the common elements to all options

Allowing entry of generic medicines as soon as market exclusivity is expired, means that an **application for authorisation** of a generic version of the medicine **can be submitted** during the protection period, and can enter the market right after expiry of the market exclusivity. Currently, generic versions of orphan medicines cannot start the authorisation process before the market exclusivity expires[167]. This creates a windfall protection of at least 9 months beyond the 10 years ME, equal to the time needed to authorise a generic medicine from submission[168]. It is estimated that 10 out of the expected 25 new orphan medicines would be impacted per year, the ones where ME is the last layer of protection. Apart from legal certainty for generics it would mean up to €360m savings to the public. Originators would lose their windfall profits by €354m. See Table 11 for the financial impacts of day-1 entry of generic medicines on all stakeholders. More details are provided in Annex 4, section 3.c.iii.

Table 11 – financial impacts of day-1 entry of generic medicines	Systemic change (10 medicines)
Originator gross profit	**-€354m**
Generic gross profit	+€50m
Cost to public payer	**-€200m**
Δ of patients treated (monetised)	+€160m
Patients + payer monetised gain/loss	**+€360m**

Abolishing the paediatric market exclusivity extension[169] for completing PIPs will better regulate a system that is currently not functioning very well. At present, the paediatric regulation offers 6 months of SPC extension for completing a PIP, and for orphan medicines 2 years of market exclusivity extension. However, there are several SPC protected orphan medicines with 13-14-15 years of protection duration[170]. For these products a 10+2 years market exclusivity is of less value and they would be better off with a 6 months extension of the SPC protection. To switch to this protection, they need to renounce their orphan designation and they often do so. The abolition of the paediatric extension of market exclusivity is thus expected to improve clarity in the system.

The measure will also imply that orphan medicines <u>not</u> protected by SPC but eligible to complete a PIP, will lose the 2-year extra market exclusivity protection available in the baseline. However, from the entry into force of the Paediatric Regulation up to 2020, only 11 of these market exclusivity extensions were granted[171], meaning that it has been a rarely used incentive. With 1 such incentive not granted per year in the future, the public would save €96m per year. The affected originator companies would lose €94m in gross profits over the medicine's lifetime each, but due to the few uses, the impact on the whole industry is not significant. More details are provided in Annex 4 section 3.c.iv.

Table 12 – Impact of abolishing 2 years ME extension for completed PIP	Systemic change (1 medicine)
Originator gross profit	**-€94m**
Generic gross profit	+€13m
Cost to public payer	**-€54m**
Δ of patients treated (monetised)	**+€42m**
Patients + payer monetised gain/loss	**+€96m**

[167] See also Section 5.2 of this SWD (common elements).
[168] This is different to the general pharma legislation, where regulatory data protection is designed in a way to allow generic filing before expiry.
[169] This measure is regulated in the Paediatric Regulation and it is mentioned as a common elements of the revision of the paediatric legislation, however it changes the market exclusivity period, therefore its impact is relevant for orphan products therefore it is discussed in this section.
[170] See also Table 3 (length of protection of orphan medicines by type of protection).
[171] EMA data.

The introduction of the global marketing exclusivity (GMA) will limit stacking market exclusivity periods for additional orphan indications and should lead to a simplification of the system. The GMA prolongs the existing market exclusivity by only 1 year in all orphan indications. The use of this incentive is maximised at two indications, i.e. maximum 2 years of prolongation of the ME will be possible. Furthermore, market exclusivity granted **to a second generation product** that is similar to the first generation product will not be applied in respect of generic products of the first reference product for which the market exclusivity expired to avoid so called evergreening[172].

The GMA would concern 16% of orphan medicines, those with multiple orphan indications. For them it would mean replacing 4.2 years of partial protection for additional indication with on average by 1.3[173] years complete protection of the medicine. Importantly, this would put a limit on 'orphan blockbusters' with several indications, and disincentives on gaming the system for artificially inflated protection periods. More details are provided in Annex 4 section 4.

Enhanced regulatory support for HUMN products will improve study designs, support developers especially SMEs and those with less regulatory knowledge, reduce assessment time and increase quality of evidence. It can ultimately allow those products come to the market earlier, provided the benefits outweigh the risks, increasing the number of new orphan medicines per year. **Companies that lose commercial interest in marketing an orphan product** will be encouraged to offer it for transfer to another company rather than withdrawing it, therefore contributing to an increased number of products staying on the market. **The capping of an orphan designation at 7-years** is expected to act as push to developers for faster translation from orphan designation to authorisation. **Abolishing the orphan designation criterion on the basis of return on investment** will reduce the regulatory burden and provide a more flexible regulatory framework. The **transfer of the responsibility for adopting decisions** on 'orphan designations' from the Commission to the Agency will provide more effective and efficient procedures.

6.1.2 Combined impact of the measures

Option A

The combined impact of the measures is shown below in Figure 4, depicting the cost-benefits of Option A on all stakeholders.

Figure 4 – cost/benefits for all stakeholders of Option A[174]

	Cost/benefit for **public payer and patients**	Cost/benefit for **originators**	Cost/benefit for **generic industry**
Option specific measures			
Keeping the baseline ME	Neutralising general pharma's access gains	0	0
Novel incentive – voucher for HUMN	+€994m additional cost +1-2 additional HUMN medicines per year	+€151m gross profit for HUMN developer +€576m gross profit for voucher buyers	- €122m gross profit

[172] See also Section 5.2 of this SWD.
[173] The weighted average of protection for medicines with one or more additional indication
[174] Public payers' costs are under 'public authority' section; originators mean marketing authorisation holders of an original version of the medicinal products, as opposed to generic industry. Interests of those SMEs, which are involved in R&D of original products, correspond to interests of originators.

Common elements			
Day-1 entry of generic/biosimilars after ME expiry	€360m cost saving	-€354m gross profit	+€50m gross profit Predictable market entry
Abolishing 2-year ME extension for completing PIP	€96m cost saving legal clarity	-€94m gross profit	+€13m gross profit
Global marketing exclusivity	cost neutral, more predictable	Shorter protection time Stronger protection =cost neutral	cost neutral, more predictable
Total balance	**+€538m extra cost** +1-2 additional HUMN medicines per year **Lower access**	**+€279m gross profit** **Unfair and inefficient distribution of profits**	**-€59m gross profit**

Conduct of business: The additional reward in the form of a transferable exclusivity voucher will increase the profits of industry (originators including SMEs), although disproportionately for the voucher *buyers* rather than for the HUMN developers in view of the potential high number of vouchers. It is therefore not expected to have positive impacts on HUMN developments. Moreover, keeping the same length of market exclusivity for all orphan medicines, which is detached from their investment costs and level of innovation addressed, may lead to overcompensation of some pharmaceutical companies. Introducing increased scientific support for HUMN would be positive for business engaged in areas of more risky research (often SMEs). All the measures aimed at the faster generic/biosimilars competition[175] are expected to have a positive effect for generic industry. As these measures are aimed to avoid unjustified benefits being drawn from the market exclusivity, the overall impact on the conduct of business would be positive.

Other common element measures aimed at improving patients' access (transfer to another company rather than withdrawing an orphan medicine; capping the duration of the orphan designation at 7 years) will be of limited effect for businesses. Still, the transfer of an orphan medicine, facilitated by publishing the intention of withdrawal, could have a positive impact on the conduct of business.

Providing for the possibility to adapt the current definition of an orphan condition to ensure that the legislation is 'fit' to embrace technological and scientific advances would have a positive impact on businesses. Removing the orphan designation criterion of return on investment will have no impact on businesses since it has never been used[176] (although it will simplify the system). Transfer of responsibility for adopting decisions on 'orphan designations' from the Commission to the Agency will create a faster decision-making and, therefore, a positive impact on conduct of business. **SMEs:** as SMEs are involved mostly in early stage of R&D and invest in riskier areas of R&D targeting innovative products, transferrable exclusivity vouchers could potentially increase the value of their research assets/authorised product once sold to big pharma, however due to the high number of vouchers, such a positive impact would be diluted.

[175] Generics/biosimilars can enter the market at day-1 of the expiry of the exclusivity period; Reduction of consecutive periods of market exclusivity for new indications of the same orphan medicine by introducing them under the same "Global Marketing Authorisation" (GMA); the market exclusivity granted to a second generation product that is similar to the first generation product shall not be applied in respect of generic products of the first reference product for which the market exclusivity expired.
[176] Section 5.1 of the Joint Evaluation.

Public authorities: The introduction of a voucher may carry a significant cost to the national authorities as longer exclusivity periods will delay entry of cheaper generics.

Impacts on R&D / innovation: The additional incentives will support increased return on investment for developers and bring additional investment into R&D for HUMN. However, in the case of vouchers a more limited impact is expected as due to the potential high number of vouchers, their value will diminish.

Administrative burden: Procedural simplifications will reduce administrative burden.

Internal market: The impact on the internal market can mainly be seen from the viewpoint of the number of new products on the market, their availability and patient's access across the EU. The new incentives would increase the number and availability of new orphan medicines. On the other hand, lack of specific measures to achieve EU-wide market launch and patient access would retain the level of fragmentation of the internal market as in the baseline. Delayed generic entry would hinder competition, and keep prices high for a longer period compared to the baseline.

Competitiveness/trade: The special incentives for HUMN, including the transferable voucher, and common measures for simplification are expected to improve competitiveness and attractiveness of the EU pharmaceutical sector, especially SMEs, and support increased investment in medicine development to address unmet medical needs.

Digital impact: Measures that are being considered in the revision of the general pharmaceutical legislation (for example the digitalisation of procedures and the possibility to analyse real world data) are expected to support pharmaceutical companies and public authorities to enjoy the benefits coming from digital innovation in the sector. The European Health Data Space[177] will provide a common framework across Member States for the access to high-quality real world health data and will be particularly relevant for small patient populations. The data, for example collected through rare disease registries, will become accessible and are expected to allow progress in research and development of medicines and provide new tools in pharmacovigilance.

Option B

The combined impact of the measures is shown below in Figure 5, depicting the cost-benefits of Option B on all stakeholders.

Figure 5 – cost/benefits for all stakeholders of Option B

	Cost/benefit for **public payer and patients**	Cost/benefit for **originators**	Cost/benefit for **generic industry**
Option specific measures			
No market exclusivity	+€725m cost savings Political signal to divest rare disease R&D likely 1-2 HUMN less per year	-€751m gross profit	+€101m gross profit
Common elements			
Day-1 entry of generic/biosimilars after ME expiry	€360m cost saving	-€354m gross profit	+€50m gross profit Predictable market entry

[177] COM(2022) 197 final.

Abolishing 2-year ME extension for completing PIP	€96m cost saving legal clarity	-€94m gross profit	+€13m gross profit
Global marketing exclusivity	cost neutral, more predictable	Shorter protection time Stronger protection =cost neutral	cost neutral, more predictable
Total balance	**€1.181m cost saving** **1-2 HUMN less medicines per year** **0% increase in access**	**-€1.199m gross profit**	**+€164m gross profit**

Conduct of business: Absence of market exclusivity is expected to result in less R&D in medicines for rare diseases, as originators will not have an incentive to engage in such R&D. Generic entries will gain faster access to the market, however, there will be also a smaller number of new original products, which could offset to some extent this gain. The impact of common elements in this option is similar as for Option A. **SMEs:** No market exclusivity will particularly negatively impact SMEs involved in R&D as they will face a high risk that no big company will be eager to buy the result of their R&D if this incentive is abolished. In consequence, they may find it too economically risky to engage in R&D of orphan products.

Public authorities: Health payers may benefit from lower average costs for medicines due to earlier generic entry. The extent of these benefits will depend on originators' response to the absence of the reward, and it is possible that average prices will be adjusted upwards to some degree to offset the elimination of the compensation mechanism. However, these savings for public authorities should also be seen in the perspective of costs related to the lack of adequate treatments (see also the following subchapter under 'social impacts of the policy options').

Impacts on R&D / innovation: The absence of a reward in the form of market exclusivity may lead to the reprioritisation of research in the area of orphan products and, hence, negatively affect investment into R&D neutralising the positive effects of the common elements for the development of new products in particular in areas of HUMN.

Administrative burden: Simplification of procedures (common elements) is expected to bring positive results.

Digital impact: The digital impact in this option is similar as for Option A.

Internal market: Earlier generic entry due to the elimination of the reward may in theory improve access, but any gains for the internal market may be offset by the absence or belated availability of new orphan products aimed at areas of HUMN and innovative orphan products.

Competitiveness/trade: Elimination of the market exclusivity could weaken the global competiveness of EU based originators compared with the current situation, which is not expected to be outbalanced by positive aspects of procedural simplifications from the common elements.

Option C

The combined impact of the measures is shown below in Figure 6, depicting the cost-benefits of Option C on all stakeholders.

Figure 6 – cost/benefits for all stakeholders of Option C

	Cost/benefit for **public payer and patients**	Cost/benefit for **originators**	Cost/benefit for **generic industry**
Option specific measures			
+1 year of ME for HUMN addressing medicines	+€82m additional cost 1-2 additional HUMN medicines per year	+€94m gross profit	- €13m gross profit
1 year of ME conditional for full EU launch	€288m cost saving from non-complying medicines (6 non-complying MP) Broader and faster access to complying medicines	-€282m gross profit loss (6 non-complying MP) +€4m additional cost (4 complying MP)	+€38m gross profit gain due to non-complying medicines (6 non-complying MP)
Common elements			
Day-1 entry of generic/biosimilars after ME expiry	€360m cost saving	-€354m gross profit loss	+€50m gross profit Predictable market entry
Abolishing 2-year ME extension for completing PIP	€96m cost saving legal clarity	-€94m gross profit loss	+€13m gross profit
Global marketing exclusivity	cost neutral, more predictable	Shorter protection time Stronger protection =cost neutral	cost neutral, more predictable
Total balance	**€662m cost saving** **+1-2 additional HUMN** **+9% broader and faster access**	**-€640m gross profit loss**	**+€88m gross profit**

Conduct of business: The modulation of market exclusivity duration is expected to target those areas where research is mostly needed and where the investments are most risky, therefore would contribute to a fairer distribution of incentives. The impact of common elements in this option is similar to Option A.

SMEs: The 10-year market exclusivity for products addressing HUMN and innovative products will benefit SMEs (active in riskier R&D). Although the 10-year market exclusivity period corresponds to the current baseline, by the fact that market exclusivity periods will be differentiated, the relative value of HUMN/innovative products will increase. As to the common elements, their costs are expected to be the same across all the options (for details see Option A).

Public authorities: The costs to national health systems are expected to increase, as compared to the baseline, due to an increase of the maximum market exclusivity periods (10 years + 1 year for the market launch in the whole EU + max. 2 years for new indications) and thus delayed entry of generics. The reduced (compared to the baseline) 5-year market exclusivity period, as applicable to products with well-established use, is not expected to result in major significant reduction of costs to public authorities costs.

Impacts on R&D / innovation: Additional ME, given for orphan products which address HUMN and innovative products will boost R&D in those areas.

Administrative burden: The impact of administrative costs is similar as for Option A, i.e. less administrative burden is expected, thanks to procedural simplifications. Some additional documentation may be required for eligibility for the HUMN category, and hence for additional ME.

Digital impact: The digital impact in this option is similar as for Option A.

Internal market: The effect on the internal market (availability and patient access) is expected to be positive due to an additional ME period for EU-wide launch as well as access-inducing measures from the common elements.

Competitiveness/trade: The system of modulated ME is expected to boost competitiveness and attractiveness of the EU pharmaceutical sector and support increased investment in orphan medicines development. The common elements such as procedural simplification are expected to have a further positive effect.

6.1.3 Social impacts of the policy options

The revision of the orphan regulation aims to meet two *societal* needs:

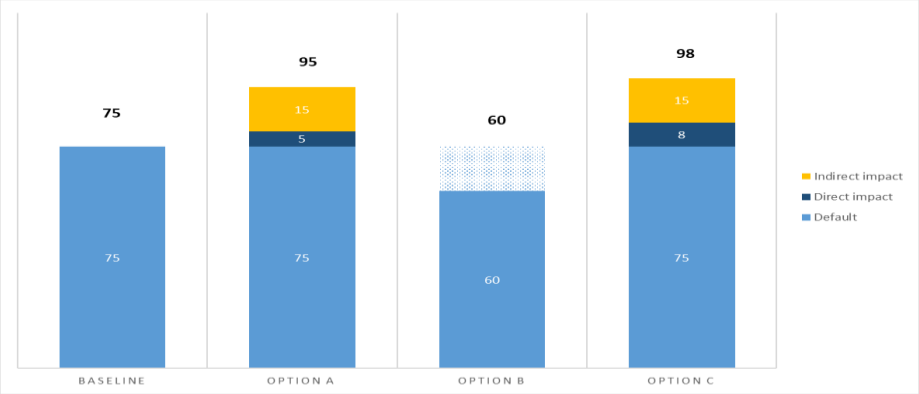
- Increase therapeutic options for rare disease patients, especially in disease areas where therapies do not exist or are insufficiently effective (high unmet medical needs - HUMN).
- Ensure better and equal patient access to medicines for rare disease across the EU.

Therefore, we measure the social impacts by two indicators: 1. Number of medicines addressing HUMN and 2. The increase in patient access.

Medicines addressing HUMN

Orphan medicines addressing HUMN can be considered more valuable to society than other new medicines, because of the lack of any existing alternative and the existing burden for patients and health systems. This does not undermine the value of development of medicines for other rare diseases as the existence of more than one therapeutic options benefit patients, health care professionals and increase competition. Figure 7 below summarises the expected change in number of medicines addressing HUMN under the different options[178].

Figure 7 - Expected number of HUMN addressing orphans in the various policy options.



Option A maintains the baseline incentives and adds the vouchers on top of it for HUMN products. It could stimulate extra investment in HUMN products. The downside of the vouchers is that it may

[178] Apart from the social impact of Options A/B/C, there is also the common element to all options of the **adaptation of the current definition of an orphan condition** to ensure that the legislation is better 'fit' to embrace technological and scientific advances. This will support the development of products in HUMN areas (and should also cater for more efficient procedures for designation and authorisation).

become a very expensive and inefficient way of rewarding developers. We estimate that compared to the baseline (75 HUMN for 15 years), the **overall number of HUMN products could go up to 80** with the additional incentive (direct impact).

Option B is not only indifferent to HUMN medicines, but it abolishes the market exclusivity, sending a negative signal to orphan medicine developers targeting the European market, namely that orphan medicines are not anymore a priority in the pharmaceutical legislation. This signal would likely trickle down to research funders, investors and national authorities, resulting in a decline in orphan medicines, and consequently a decline in HUMN medicines too. **An estimated 20% decline in newly authorised orphan medicines** would bring down the number of **HUMN addressing orphans to 60** in the next 15 years.

Option C offers a modulation of market exclusivity period, favouring medicines addressing HUMN and rewarding them with 1-year additional protection. This translates into a 14% higher protected revenue, or 7.7% higher gross-profits compared to other medicines, making their development and authorisation more rewarding commercially. Overall, the incentive could directly **increase the number of HUMN addressing medicines by 10%, to 83** in the next 15 years (*direct* impact).

We can expect that both **Option A** and **C** will also have important *indirect* impacts. An EU level definition of HUMN under the common elements could lead to important spill-over effects, just as it happened with the introduction of the orphan designation in the EU Orphan Regulation in 2000[179].

All these spill-over effects led to a successful market creation that boosts investment and innovation. A definition of HUMN would therefore allow labelling research and medicinal products that have highest utility for society, and channel public resources – either research funding or favourable P&R conditions – towards them. The extra benefit given for HUMN in the orphan regulation would showcase the EU's commitment, and invite other actors to follow suit in their own realms.

Improving access to orphan medicines

The revision of the *general* pharma legislation proposes a solution where 1 year of additional regulatory protection would be granted in case the medicine is launched in all EU countries within 2 years from authorisation. According to the analysis conducted in the impact assessment of the general pharmaceutical legislation[180], this not only would increase the number of Member States with access (and thus the percentage of the EU population covered), but the medicine would also be made available for more people in a significantly shorter time than in the baseline.

Option A by keeping the market exclusivity at 10 years without any modulation, would nullify the access conditionality introduced in the general pharma legislation. Option A would therefore equal the current status quo (baseline).

Option B, which abolishes market exclusivity, would leave the protection period defined only by the general pharma for orphan medicines. The general pharma legislation will incentivise access, and it is worthwhile for companies to make an effort to launch in all Member States. Option B should result in higher and faster access than the baseline.

[179] At the time, an important win for orphan developers was not the market exclusivity alone, but also the recognition of rare diseases by many different actors. National and international research funders, notably EU's Horizon and its predecessor framework programmes, started providing dedicated funding for rare disease research after this recognition. Furthermore, national HTA and pricing & reimbursement authorities recognised that orphan medicines deserve more flexible and tailored rules, creating favourable market conditions for them. And European Reference Networks (ERNs) were established to improve rare disease patients' access to expertise, diagnosis and treatment across the EU. See also Section 1.3 of this SWD.

[180] Staff Working Document – Impact assessment on the general pharmaceutical legislation (Annex 4)

Option C modulates the market exclusivity mirroring the general pharma. Thus, it would preserve the incentive for improving access, just from a higher basis (9 year default market exclusivity vs. 8 year default regulatory protection). We expect therefore a similar impact for option B and C.

Figure 8 – Percentage of population served over time

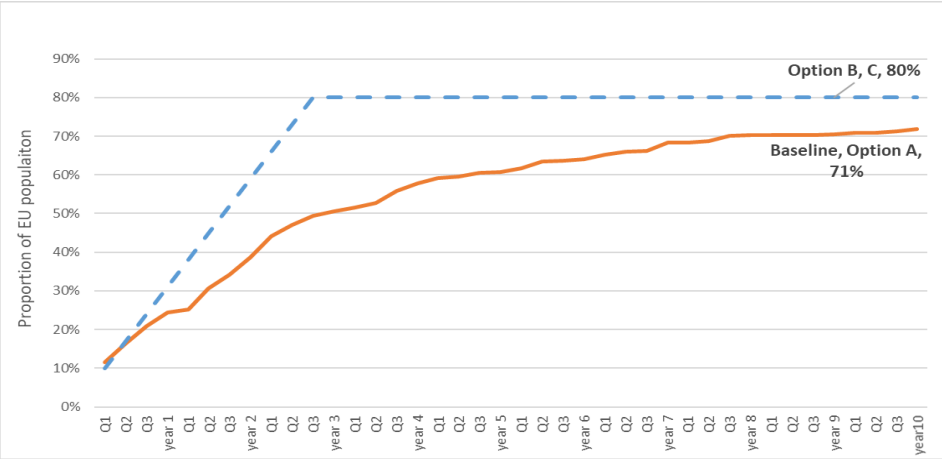


Figure 8 demonstrates the expected impacts of the various policy options on patient access[181]. Option B and C reach a higher plateau of 80% EU population covered, and also much faster than Option A/baseline, two years following authorisation.

Stakeholder views on HUMN and access

All stakeholder groups were in favour of better focus on HUMN. However, **pharmaceutical industry** is not in favour of strict HUMN criteria whereas **health payers/public authorities** support this idea. **Pharmaceutical industry** is strongly against linking the provision of the market exclusivity with launching obligations, whereas health payers/public authorities were mixed in their views. Other common elements (enhanced regulatory support for HUMN products, addressing regulatory limitations, possibility to transfer a marketing authorisation to another company rather than withdrawing, capping of an orphan designation at 7-years) were overall supported by all stakeholder groups.

6.2 Medicines for children

6.2.1 Economic impacts of the policy options

The economic impacts of the policy options on the main stakeholders (industry, public authorities, patients) has been assessed and quantified by focusing on: a) assessing the potential effects of changes to the extension of the SPC under the various options (including the introduction of a novel reward under option A); b) assessing the impact of the common elements. Other economic impacts have been considered and they are detailed here below by stakeholder group.

Public authorities derive benefits in the form of savings from avoided hospitalisation and avoided outpatient treatments due to the reduced number of products tested and authorised for use in children Such benefits were calculated in the Joint Evaluation on the basis of paediatric products developed and resulted in minor, almost irrelevant impacts therefore these benefits have not been considered in the current economic analysis (more details are provided in the social impact section). Concerning the costs, they are impacted by the costs of medicinal products linked also to the length of

[181] It is hereby important to keep in mind that these incentives work with medicines that are not protected by SPC or patents, as those IP incentives provide longer protection than the maximum achievable market exclusivity for more than half of all newly authorised medicines.

protections which delays the entry of generic medicines. The proposed options are not expected to produce administrative costs for public authorities.

The **innovative pharmaceutical industry** incurs two types of costs: clinical research costs linked to the obligation to study any new medicines for use in children and administrative costs linked to the PIP procedure. The options proposed are not expected to impact the costs of conducting paediatric studies but are instead expected to have an impact on the administrative costs linked to PIPs. Industry benefits derive from the rewards provided for the completion of the paediatric studies and the sale of the products. The **generic industry** is not concerned by the PIP obligations and they have no obligation to include paediatric indications or formulations developed by the originators. The SPC extension delays generic competition by 6 months, but this is not necessarily revenue lost, rather delayed. The generic industry is concerned more by the non-predictability of the SPC system (which is regulated by a separate piece of legislation[182] currently under revision and where a unitary SPC system has been explored) due to the different handling by each national patent office than by the SPC extension in itself. The impact of the elimination of the extension of two extra years of marketing exclusivity for paediatric orphan medicines with completed PIP is analysed in Section 6.1.1.

Patients' costs and benefits derive from delayed/faster access to the products developed. Other impact on patients are assessed in the social impact section.

Which medicines are affected by changes in SPC extension?

The paediatric regulation's key feature is the obligation for medicine developers to carry out PIPs and the reward that it offers in form of SPC extension to compensate the companies' efforts[183]. The policy options in the current revision offer different duration of the SPC extension. Analysing our basket of medicines from the IQVIA database[184] reveals that 20% of newly authorised medicines have claimed and used the incentive in the recent past[185]. We, therefore assume that 10 medicines per year will receive the extension 15 years from now.

Table 13 - Comparison of medicines with paediatric extension to medicines without extension

	Number of products	Avg. protection period	Avg. peak annual revenues
Medicines with paediatric extension	40 (20%)	14.3 years	€ 540.6 m
All other medicines	159 (80%)	12.7 years	€ 199.5 m

Table 13 also demonstrates, that the medicines benefitting from the SPC paediatric reward generate far higher revenues than those that do not benefit from this. More details in Annex 4 section 7.

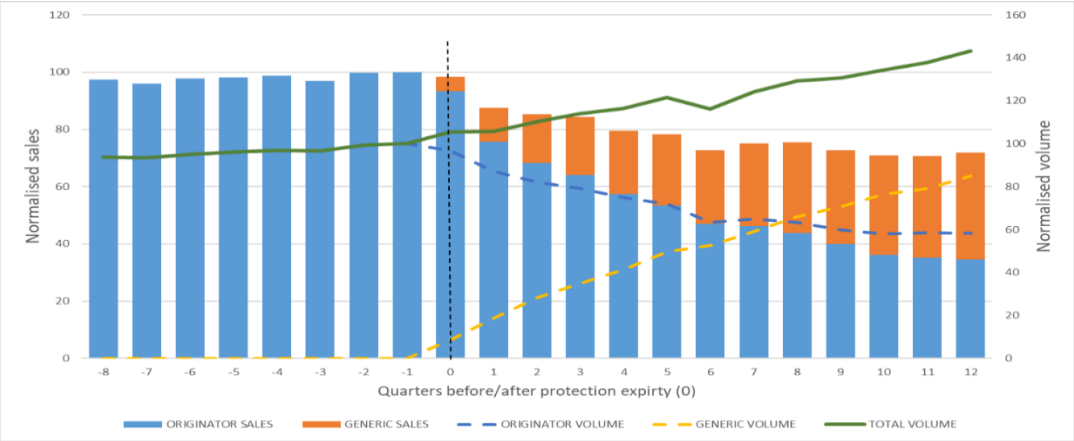
How the SPC extension generates value/cost for stakeholders

In analysing the impacts of changes in the SPC extension, we use the same model as for the general pharma and orphan medicines. The model represents an innovative medicine, an analogue, for which the paediatric SPC extension is the last layer of protection from generic competition. To create this

[182] Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the supplementary protection certificate for medicinal product.
[183] Section 5.2.4 of the Joint Evaluation finds that the average cost to complete a PIP is around €20 million.
[184] The same cohort of medicines that was used in the general pharma and for orphan medicines, a basket of 199 medicines with protection expiry between 2016 and 2024.
[185] The IQVIA database does not specify which medicines were subject to the PIP obligation of were granted a deferral. It should also be considered that for some products the PIP was not yet completed at the moment of the MA and therefore the SPC extension could not yet be claimed. Delays in receiving the SPC extension from national patent offices cannot be ruled out.

analogue, historical data[186] were used. More details in Annex 4 section 7.b. The sales of the originator products and their generic/biosimilar competitors from 2 years before to 3 years after protection expiry were analysed in Figure 9 below.

Figure 9 - Modelling generic entry after SPC extension expiry



The model uses normalised units to represent prices and volumes across different products, where 100 is equal to originator's peak sales, at quarter -1 (the last quarter before generic/biosimilar competition)

As shown in Table 13 below, medicines benefiting from SPC paediatric extension are generally characterised by high sales, they are prime targets for generic/biosimilar competition. Here we see more competitors coming after protection expiry, a more aggressive substitution of originators by generics/biosimilars and a steeper price erosion (and public cost saving) after expiry. The stakes are also higher both for companies and public payers, one year monopoly means a lot of profit/lot of public cost. More details in Annex 4 section 7.e).

Option A – 6 months SPC extension + novel incentives

Option A proposes extra incentives if a PIP is completed for a product that addresses an unmet medical need (UMN). We expect that 20% of the new products will meet the UMN criteria[187], therefore out of the expected yearly 10 SPC extension, 2 would be for UMN addressing medicine. One measure considered is to give +12 months SPC extension for these products, instead of the current +6 months. The economic impacts of such a measure on the different stakeholders, estimated using the model set out above, are presented both for a single product, and at systemic level (for the 2 benefiting products) in Table 14. Annex 4 section 7.c presents the detailed calculations.

Table 14 - impact of 6 months protection increase (+12 months SPC extension) for UMN on different stakeholders

	avg product (€540 m annual sales)	Systemic impact (2 extensions/year)
Originator gross profit	**+€169 m**	**+€338 m**
Generic gross profit	-€32 m	-€64 m
Public payer's gain/loss (cash)	-€78 m	-€156 m
Δ of patients treated (monetised)	-€78 m	-€156 m
Patient and payer gain/loss	**-€156 m**	**-€312 m**

[186] A basket of 11 products with paediatric SPC extension expiry between 2016 and 2018 served the basis of the analogue

[187] Based on historical data of how many products authorised for use in children would qualify as UMN products.

Thus, benefiting originator companies would increase profits by €338 m at a cost of €312 m to the public.

The analysis of the impact of the introduction of a regulatory protection voucher for medicines addressing UMN is provided in section 6.3 (orphan option A). It concludes that if there are high numbers of vouchers distributed, it becomes a costly and ineffective instrument and this is *a fortiori* applicable for paediatric medicines[188]. More details in Annex 4 section 5).

Stakeholder views: the possibility of increasing the protection of products completing PIPs is supported at least partially by industry and some researchers. For example industry would favour an increase in the rewards if an obligation to conduct PIP on the basis of the mechanism of action of their product would be introduced. Some researchers and patients organisation would favour an increased reward for development in some specific areas, for example rare paediatric cancers. Competent authorities oppose to any additional rewards in particular under the form of vouchers.

Option B – no SPC extension

Under option B, medicines which would currently be eligible for the 6-months SPC extension will lose such protection. Generic medicines could enter the market earlier and public authorities would pay less, for more patients served. We have adjusted our model to the new expiry and compared it to the baseline. Table 15 shows the impact of the change for all stakeholders, both at an individual product level, and at systemic level for all 10 products, that would benefit from the extension in the baseline.

Table 15 - impact of 6 months protection reduction on different stakeholders

	avg product (€540 m annual sales)	Systemic impact (10 extensions/year)
Originator gross profit	**-€169 m**	**-€1,690 m**
Generic gross profit	+€33 m	+€330 m
Public payer's gain/loss	+€76 m	+€760 m
Δ of patients treated (monetised)	+€75 m	+€750 m
Patient and payer gain/loss	**+€151 m**	**+€1,510 m**

At an individual product level, the reduction is a significant loss to the **originator company**, an average SPC extended product would lose -€169 m gross profit. The **generic** products would have +€33 m higher profits thanks to the earlier entry. The **public payer** would experience +€76 m yearly savings, however this is not the only benefit for the public. Not only the total cost would be less, but more **patients** could be served with the more affordable medicine, adding an additional +€75 m monetised patient benefit. Overall the public gains €151 m thanks to the reduction. Looking at systemic level, the loss of 10 SPC extensions compared to the baseline would cause €1.690 m profit loss to the innovator industry annually. On the other hand, the public would make significant savings, to the tune of €1,510 m per year. More details in Annex 7 section 7.d.

Stakeholder views: During the stakeholder consultation none of the stakeholder groups supported the abolishment of the SPC extension. There is a broad consensus that the paediatric regulation works overall well, delivers the needed studies for children, and the incentive is perceived as a significant element of the good performance.

Option C – 6 months SPC extension

[188] Looking at historical data 30% of products authorised with paediatric indications could be classified as fulfilling the UMN criteria.

Option C preserves the baseline SPC extension reward, therefore compared to the baseline this measure has a neutral economic impact. Despite not changing the SPC extension, together with the common elements option C could tackle the objectives of the revision.

Impacts of common elements

Support for products addressing UMN – The possibility to benefit from dedicated research funding and later by early support by the Agency for products considered as having the potential to address UMN of children, is expected to increase the number of these products authorised for use in children. The measure is also expected to increase predictability of the outcome of their development for companies and be advantageous in particular for SME who may be facilitated in raising capitals from investors for these products.

Evolutionary PIP - This streamlined process could affect up to 25-30 % of the procedures. There would be an increased effort for EMA's Paediatric Committee (+ 10-20 %), but a reduced burden for industry (30%) due also to a better alignment with the US system. This measure is expected to positively influence SMEs, as they are more likely to benefit from lower administrative burdens respective to their scale and ability to bear sunk costs as part of their business model.

Simplified PIP - A less demanding PIP could be granted in selected situations such is the case of the paediatric only products to reduce burden and timing of the PIP preparation and application. A simplified PIP may also be used for PUMA products. It is difficult to predict the impact of the measure as it cannot be anticipated the number of paediatric only products which will be submitted. However, it is expected to have a similar impact on SMEs as the Evolutionary PIP.

The change in the waiver system to take into account the **mechanism of action** of a product has been estimated that it would lead to 8.3% more PIPs, including the UMN ones. This would translate into 3 additional PIPs per year, and 1 additional SPC extension reward. This measure is also expected to encourage the use of digitalised methods of genetic screening of the causes of diseases by the industry and academics, affecting SMEs more than larger pharmaceutical companies. The measure would require also SMEs to study a product on diseases where they do not have the necessary knowledge/expertise available in house and consequently increase their costs.

Cap in the maximum length of the duration of the deferrals which can be granted to completion of a PIP. This element is expected to reduce the average duration of 18% of PIPs.

6.2.2 Combined impact of the measures

Option A

	Cost/benefit for **public payer and patients**	Cost/benefit for **originators**	Cost/benefit for **generic industry**
Option specific measures			
Additional 6 months SPC extension for UMN	+€156m cost	+€338m gross profit	-€64m gross profit
Common elements			
Mechanism of action	3 more PIPs +€151m cost resulting from additiona1 SPC extension	+€169m gross profit +€66m cost	-€33m gross profit
Cap in the maximum length of the deferrals	Faster completion of PIPs Cost neutral	Cost neutral	Cost neutral
Total balance	**+€307m cost** **+3 PIP** **+earlier access**	**+€441m gross profit**	**-€97m gross profit**

Conduct of business: The higher reward compared to today for the completion of PIPs would have a positive effect on businesses that invest in products addressing UMN. However, the introduction of

a voucher system is not considered to have positive impacts on developers of the UMN products due to the potential high number of vouchers; it may even undermine the use of such a scheme in the area of antimicrobials. Moreover, this option could negatively impact the generic and biosimilar industry as it would further delay their access to the market. No specific effect from this option is expected for SMEs. Originators will incur into extra costs for conducting on average 3 extra PIP/year due to the introduction of the mechanism of action provision[189].

Public authorities: The introduction of an additional reward providing longer protection periods may carry a significant costs to national health systems and payers by delaying generic entry.

Impacts on R&D / innovation: The additional incentives will support increased return on investment for developers and bring additional investment into R&D for UMN. However, in the case of vouchers a more limited impact is expected as due to the potential high number of vouchers, their value may be low.

Administrative burden: Reduction is expected to derive from the common elements. In particular:

- *Evolutionary PIP:* This streamlined process could affect up to 25-30 % of the procedures. There would be an increased effort for EMA's Paediatric Committee (+ 10-20 %), but a reduced burden for industry (30%) due also to a better alignment with the US system.
- *Simplified PIP:* A less demanding PIP could be granted in selected situations, such is the case of the paediatric only products, to reduce burden and timing of the PIP preparation and application. A simplified PIP may also be implemented in case of PUMA products. It is difficult to predict the impact of the measure as it cannot be anticipated the number of paediatric only products which will be submitted.

Digital-by-default / digital ready policy making: The introduction as a common element of the obligation to take into account the molecular mechanism of action of a product when designing a PIP are expected to encourage the use of digitalised methods of genetic screening of the causes of diseases by the industry and academics

Internal market: While the increases in the number of new medicines for children owing to the new incentives provided improve the functioning of the internal market, delayed generic entry would hinder competition, and keep prices high for a longer period compared to the baseline.

Competitiveness/trade: The special incentives for UMN, including the transferable voucher and EU-wide market launch are expected to improve competitiveness and attractiveness of the EU pharmaceutical sector and support increased investment in medicine development to address UMN. The common elements evolutionary PIP and the consideration of the mechanism of action of a product in the design of a PIP would bring the European system close to the system in place for medicines for children in the US, therefore increasing the competitiveness of the EU pharmaceutical sector as companies tend to operate globally

Option B

	Cost/benefit for **public payer and patients**	Cost/benefit for **originators**	Cost/benefit for **generic industry**
Option specific measures			
Maintaining current extension	€1.510m cost saving	-€1.690 m gross profit	+€330m gross profit
Common elements			

[189] The costs of the conduction of a PIP has been estimated in around 22m euro. Joint evaluation of the orphan and paediatric regulation.

Mechanism of action	3 more PIPs	+€66m cost	0
Cap in the maximum length of the deferrals	Faster completion of PIPs Cost neutral	Cost neutral	Cost neutral
Total balance	**+€1.510m cost saving** **+3 PIP** **+earlier access**	**-€1.756m gross profit** **No compensation for carrying out PIPs**	**+€330m gross profit**

Conduct of business: The elimination of the reward for the completion of the PIP will mean that companies have to cover the costs for the paediatric development themselves and can no longer count on the reward as a compensation for clinical studies stemming from the paediatric legislation. Generic and biosimilar industry may benefit from slightly earlier market entry by 6 months. However, the generic biosimilar version may not necessarily include the paediatric formulations (generics have no obligation to develop and market paediatric adapted formulations of their products) hence not serving children. The deletion of the SPC extension would negatively affect in particular SMEs as they may find it more difficult to raise funding due to the possible non/low profitability of their products.

Public authorities: Health payers may benefit from lower average costs for medicines due to earlier generic entry. The extent of these benefits will depend on originators' response to the absence of the reward, and it is possible that average prices will be adjusted upwards to some degree to offset the elimination of the compensation mechanism.

Impacts on R&D / innovation: The absence of a reward for public research may negatively impact the quality and lead to the deprioritisation of paediatric research for some products and hence negatively affect investment into R&D neutralising the positive effects of the common elements for the development of new products in particular in areas of UMN for children

Administrative burden and digital by default: similar as for option A.

Internal market: Earlier generic entry due to the elimination of the reward may in theory improve access, but this does not concern paediatric versions of those medicines as generics have no obligation to develop and market paediatric formulations. Hence, any gains for the internal market would be offset by the absence or belated availability of paediatric versions of adult products.

Competitiveness/trade: Elimination of the SPC reward could weaken the global competiveness of EU based originators compared with the current situation. It may moreover decrease attractiveness, as the obligation would be maintained without any reward.

Option C

	Cost/benefit for **public payer and patients**	Cost/benefit for **originators**	Cost/benefit for **generic industry**
Option specific measures			
Maintaining current extension	Cost neutral	Cost neutral	Cost neutral
Common elements			
Mechanism of action	3 more PIPs +€151m cost (1 SPC extension)	+€169m gross profit +€66m cost	-€33m gross profit
Cap in the maximum length of the deferrals	Faster completion of PIPs Cost neutral	Cost neutral	Cost neutral
Total balance	**+€151m cost** **+3 PIP** **+earlier access**	**+€103m gross profit**	**-€33m gross profit**

Conduct of business: Under this option, companies will obtain the same reward as in the baseline. The common elements will support companies to develop products in particular in areas of UMN.

Early support mechanism is expected to be beneficial in particular to SMEs. Compared to the baseline, generic and biosimilar industry would not be affected.

Public authorities: The costs to national health derives from the additional products that are expected to be developed due to the introduction of the common elements (mechanism of action in particular).

Impacts on R&D / innovation: R&D investment in paediatric medicines should at least reach the baseline level, but the common elements may add additional flexibility in conducting such research, facilitating its successful completion and increase output by in terms of innovative products.

Administrative burden and digital by default: similar as for option A.

Internal market: The effect on the internal market in not expected to change compared to the baseline, both for originators and generic companies.

Competitiveness/trade: Maintaining the reward are expected to keep the competitiveness and attractiveness of the EU pharmaceutical sector and support increased investment in paediatric medicine development. The common elements evolutionary PIP and the consideration of the mechanism of action of a product in the design of a PIP would bring the European system close to the system in place for medicines for children in the US, therefore increasing the competitiveness of the EU pharmaceutical sector as companies tend to operate globally.

*6.2.3 **Social impacts***

In terms of social impacts the objectives of the revision are clear: they desire more medicines available for use in children and as quickly as possible. Therefore, we measure the impacts by two key indicators, number of completed PIPs (and of them in UMN) and the speed of completing them.

Number of completed PIPs (including for UMN)

Option A would offer a higher protection for UMN addressing medicines on the top of the potential rewards from general pharma and orphan regulation (if orphan medicine). However it is questioned whether this incentive would indeed foster new PIPs, or only reward PIPs in UMN, that in any case would have been carried out. If the latter, option A offers limited benefit in terms of new PIPs. **Option B** would scrap the SPC paediatric extension. The elimination of the rewards for the completion of the paediatric clinical studies is expected to neutralise the positive effects of certain common elements (for example the early support by the agency for UMN products, dedicated R&D funding for these products). It is also expected to induce companies to downscale their paediatric research programs and departments. Developers would not be encouraged to initiate the development products specific for children due to the lack of specific rewards compensating the higher costs of engaging in clinical development in children. **Option C** would keep the benefits of the baseline scenario. However some common elements and in particular introducing PIPs based on the mechanism of action would lead to 8.3% more PIP. Due to the fields that are more prone to mechanism of action PIPs (oncology, neurology, immunology), we expect that a high share of these new PIPs would be for UMN.

Timely completion PIPs and timely access for patients

Option A is not considered to differ from the baseline from what concerns the timely completion of PIPs. **Option B** may delay the developments of medicines for children as companies would not be encouraged to complete quickly a PIP in order to be able to benefit from a reward. For this reason the also authorisation of medicinal products for children is expected to decrease compared to the baseline. PIPs may be completed with a longer delay compared to today. **Option C** together with the common element that caps the maximum lengths of the deferrals it is expected to speed up by several years the completion of PIPs. Other common elements simplifying and streamlining the procedures would also translate into faster development.

6.3 Impact common to orphan and paediatric medicines

*6.3.1 **Environmental impacts***

They mainly result from their manufacturing, use and disposal, therefore is dependent from the number of products manufactured and placed on the market No specific impact derives from the measures proposed in revision of the legislation on medicines for rare diseases and for children. For this reason, no climate consistency check was conducted for this impact assessment. Measures to reduce the environmental footprint of the pharmaceutical product lifecycle are included in the revision of the *general* pharmaceutical legislation (**specific objective 4**).

These measures cover the strengthening of the environmental risk assessment as well as promoting prudent use of medicines (antimicrobials, supporting sustainable consumption, manufacturing for instance). The environmental objectives will be monitored focusing on the presence of medicines residues in the environment and on greenhouse gas emissions of EU based pharmaceutical manufacturers.

6.3.2 Impact on fundamental rights

Options A and C of both orphan and paediatric legislations, compared to the baseline are expected to have a positive impact on the **fundamental right** of patients to benefit from medical treatments under the conditions established by national laws. Those options are also consistent with the aims of the Charter of Fundamental Rights of the EU, in particular article 24 (right of children) and article 35 (health care).

7 HOW DO THE OPTIONS COMPARE?

The comparison of the policy options in relation to the baseline scenario was performed in terms of the options' overall effectiveness, efficiency, coherence, EU-added value and proportionality and taking into consideration stakeholder views.

7.1 Orphan medicinal products

7.1.1 Effectiveness

Table 16 - Overall comparison of the policy options for orphan products in terms of effectiveness

Effectiveness: contributing to achieving the policy objectives	**Baseline**	**Option A**	**Option B**	**Option C**
Objective 1: Foster innovation and R&D	0	+	-	++
- in particular for highest unmet medical needs	0	++	-	++
Objective 2: Affordability	0	--	++	+
Objective 3: Patient access	0	+/-	+	++
Objective 4[190]: Embrace scientific advances & efficient procedures	0	++	++	++
Overall social impacts	0	+	--	++
Number of HUMN products	0	+	--	++
Increase of patient access	0	--	+	++

Estimated impact compared to the baseline: + + positive, + moderately positive, –/+ neutral, – moderately negative, – – negative and – – strongly negative

[190] Objective 4 is mostly addressed by common elements to all options.

In terms of **the effectiveness** in achieving the four policy objectives, **Option C** is the most effective, as presented in Table 16 above.

On objective 1, Option C is to be the most effective in stimulating **research and innovation** of orphan medicines due to its more effective incentive to stimulate developments especially in areas of HUMN. **Option A** offers a novel incentive which likewise also focuses on the development of HUMN orphan medicines. **Option B**, which eliminates market exclusivity, would lead to fewer orphan medicines, thus being less effective. The **introduction of HUMN criteria**[191] and **enhanced regulatory support** by the Agency, under the common elements to all options will further support the overall development of products in HUMN areas.

Social impacts have been measured in relation to **objectives 1 and 3**. In this regard, the analysis mainly focused on the impact of a disease on a patient's life and health considering two main indicators: **increase in the number of HUMN products authorised** and improvement of **patient access**. **Option A** is expected to result in a fairly high total number of products addressing orphan diseases including for HUMN but will not improve patient access (as there is no conditionality between the provision of the incentives and patient access). **Option B** should lead to fewer orphan products including for HUMN and will not directly contribute to patient access. On the contrary, **Option C** should lead to more HUMN products and also to better patient access (due to the access conditionality for the extension of the market exclusivity).

As regards **objective 2**, **Option B** is the most effective as it should foster more and faster generic competition. In turn, this would benefit to the sustainability of health systems/patients as cheaper competitor products would come earlier on the market. **Option A** would be the least effective, as it keeps the current 10 years of market exclusivity and adds an extra incentive (transferable regulatory data protection voucher) thereby increasing the costs to health systems/patients and delaying possible generic competition. **Option C**, on the contrary, would incentivise products in areas of HUMN and promote earlier market entry for other categories of orphan medicinal products. The introduction of a Global Marketing Authorisation and measures to foster faster generic/biosimilar entry of competitor products, all under the **common elements to all options**, are also going to support affordability for payers/health systems.

Regarding **objective 3**, **Option C** is the most effective to ensure **timely access** in more Member States thanks to the combination of a variable market exclusivity scheme for different product categories and incentives for companies to make orphan medicines accessible in all Member States. **Option A** falls short in comparison as transferrable voucher schemes lead to delayed entry of generics, high financial burden of Member States and thus will not improve the existing uneven access to (orphan) medicinal products across the EU. **Option B,** while allowing earlier market entry of alternatives, will overall lead to fewer products developed due to the elimination of the market exclusivity. Actions to foster faster generic/biosimilar competition and measures (encourage companies that lose commercial interest in an orphan medicine to sell it to another company; capping the duration of the orphan designation), under **the common elements**, are also going to support better patient access.

On **objective 4**, all options perform in a similar manner. Measures such as providing for more flexible criteria to better define an orphan condition, streamlined procedures for designation and authorisation of orphan medicines, scrapping the orphan designation criterion on the basis of insufficient return on investment and transferring the responsibility for adopting decisions on orphan designations to the Agency are all included in **the common elements**. Furthermore, the introduction of a Global Marketing Authorisation should also lead to a simplification of the system.

[191] These criteria will identify products addressing HUMN that will subsequently profit from longer or more generous regulatory incentives under the various options.

These measures are intended to embrace scientific advances and provide more effective and efficient processes and procedures.

7.1.2 Efficiency

Table 17 - Overall comparison of the policy options for orphan products in terms of efficiency

Efficiency: comparison of benefits and costs	**Baseline**	**Policy Option A**	**Policy Option B**	**Policy Option C**
Overall costs and benefits	0	+/-	+/-	++
Administrative costs	0	+	+	+
Impact on SMEs	0	+	-	+

Estimated impact compared to the baseline: + + positive, + moderately positive, –/+ neutral, – moderately negative, – – negative and – – strongly negative

As regards the savings and benefits of the various options, **Option A** is the most expensive for health systems/patients due to the introduction of a novel incentive (regulatory data protection vouchers) and the most generous for pharmaceutical industry due to the same novel incentive. It leads to an overall €538m of extra yearly costs to public payers, while generating €279m of extra profits for originators (and a yearly loss of €59m for generic industry[192]). **Option B** creates savings to health systems/patients, but fails to deliver substantial benefits on access and on rewarding pharmaceutical industry for innovation (including HUMN products). It leads to an overall €1.181m of yearly cost savings for public payers/patients, to a yearly loss of €1.199m profits for originators, and profits of €164m for generic industry[193]. **Option C** is the most **cost-efficient**. It will bring some savings to the health systems compared to the baseline (together with the measures to foster faster generic/biosimilar completion under the common elements). At the same time it also brings the most *benefits* in terms of patient access and the development of products addressing HUMN. In monetary terms, the overall impact is €662m of yearly cost savings to public payers/patients, 640m of profit loss to originators and 88m of profit gains for the generic industry.

As regards **administrative costs**, the impacts for companies are expected to derive mostly from the common elements. Savings will come from streamlined procedures for the designation and authorisation of orphan medicines, scrapping the orphan designation criterion on the basis of insufficient return on investment and transferring the responsibility for adopting decisions on orphan designations to the Agency. Concerning the impact **on SMEs**, all **options** are expected to have a positive impact thanks to the common elements and the (additional or graduated) incentives especially for the development of products addressing HUMN (**Options A** and **C**). On the contrary, the abolition of the market exclusivity (**Option B**) is expected to have a negative impact on SMEs as they may find it more difficult and less rewarding to start the development of orphan medicinal products.

7.1.3 Coherence

Table 18 - Overall comparison of the policy options for orphan products in terms of coherence

Criteria	**Baseline**	**Policy Option A**	**Policy Option B**	**Policy Option C**
Coherence	0	+	+/-	+

Estimated impact compared to the baseline + means that the assessment is positive, and – means that it is negative

[192] See Section 6.1.2 for the combined (monetary) impact of the policy options including cost-benefit tables for all stakeholders per option.
[193] Idem.

In terms of **coherence**, all policy options were assessed with regards to their external and internal coherence. As regards the *external* coherence, the interaction of the Orphan Regulation with other EU legislative acts[194] was assessed and its interaction with national plans and strategies. All the three options were considered to be externally coherent. Furthermore, it was also explored how the policy options align with related measures taken at national level by Member States[195]. In relation to these national measures, it was found that significant heterogeneity exists in the state of advancement of national policies, plans, or strategies for rare diseases[196].

Internal coherence mostly related to the interaction with the revision of the general pharmaceutical legislation. Options A and C are internally coherent with this revision as the market exclusivity is kept or modulated under these options whereas Option B is not coherent (due to the elimination of the market exclusivity). Furthermore, all three policy options are internally coherent with the revision of the general pharmaceutical legislation[197].

The current overall system of regulatory procedures and incentives provided by the general pharmaceutical and specific orphan legislation has been considered as 'working in a coherent way' on the basis of the perceived effect by stakeholders interviewed[198]. Furthermore all options are expected to be coherent with external activities and contribute to the achievement of SDG 3 ("health and well-being") and SDG 9 ("innovation and infrastructure").

7.2 Medicines for children

7.2.1 Effectiveness

Table 19 - Comparison of policy options in term of effectiveness – medicines for children

Criteria	Baseline	Policy Option A	Policy Option B	Policy Option C
Effectiveness: contributing to achieving the policy objectives				
Objective 1: Foster investment in research and development of medicines for children	0	+	-	+
in particular for unmet medical needs	0	++	-	+
Objective 2: Create a balanced system for pharmaceuticals in the EU that promotes affordability for health systems while rewarding innovation	0	--	+	+
Objective 3: Increase patient access to medicines for children	0	+	-	+
Objective 4: Streamline processes and reduce administrative burden	0	-	+	+
Effectiveness: other impacts Social impact				
Timely completion of PIPs	0	+	-	+
Number of completed PIPs	0-	+	-	+

Estimated impact compared to the baseline: + + positive, + moderately positive, 0 neutral, – moderately negative, – – negative and – – strongly negative

[194] Regulation (EU) 2018/781 on similarity; Regulation (EC) No 2141/96 on the examination of an application for the transfer of a marketing authorization for a medicinal product; Regulation (EC) No 2141/96 on application for the transfer of a marketing authorization; Council Regulation (EC) No 297/95 on fees.
[195] Nearly all the Member States have adopted a national plan or strategy for rare diseases as of October 2021, except Malta and Sweden.
[196] No data was found to further explore the link between these national plans and the proposed options.
[197] For instance, they both provide a definition for (H)UMNs and create links between specific research priorities and the provision of incentives; they both push for innovations reaching the market more quickly through timely approval and the introduction of an access conditionality; they both simplify regulatory and administrative procedures.
[198] See also Annex 2: Stakeholder consultation (synopsis report).

On objective 1, **Option A** performs best. Thanks to the introduction of novel incentives for products addressing the UMN of children, in parallel to the 6 months SPC extensions for all paediatric products, together with the effect resulting from certain common elements (for example, the waiver system which takes into account the mechanism of action of a product and a better support for early development of UMN products) is expected to results in the highest number of products developed in particular in areas of UMN. At the opposite, **Option B** is expected to result in a decrease of products as the removal of the reward for the completion of the PIP may discourage in particular small companies or academics to start research and development in areas which could be beneficial for children. **Option C**, is expected to result in an increased number of products including addressing UMN of children compared to the baseline, thanks to the action of certain common elements. However to a lower extent than option A, as the reward for products completing a PIP will remain unchanged (6 months SPC extension).

As regards **objective 2**. The affordability of medicines for children depends from the corresponding adult medicines. However, any modification of the length of the paediatric SPC extension, which covers not only the "paediatric" medicine but also the "adult" part of a product , would have an impact on the timing of the generic entry and consequently on affordability. The introduction of additional rewards for products addressing UMN of children in **Option A**, is expected to result in a delayed generic entry for these products and therefore result in the highest impact for the health systems. **Option B** is expected to create savings for health systems compared to the baseline due to the abolition of the reward for the completion of a PIP resulting in an early generic entry. However, it will not ensure that children will be able to benefit of this improved affordability as often generic products do not cover specific paediatric preparations, dosages, pharmaceutical forms. The originator product remains the only available source even after the expiry of the protection period. While the price of originator decrease following generic entry, the lack of competition for certain paediatric formulations and preparations cannot guarantee that affordability will be achieved for medicine for children. **Option C** is expected to result in small improvement for what concern affordability compared to the baseline, thanks to common elements which by reducing the costs related to a PIP (for example by introducing early support for products addressing UMN or simplifying and streamlining the PIP process,) may results in lower prices of the product.

Regarding **objective 3**, the streamlining and simplification of the PIP system and the capping of delays under which PIP have to be completed are expected to result in a faster conclusion of the PIP and indirectly to a faster access for patients for **Options A and C**. In **Option B**, the removal of the rewards for the completion of the PIPs, is expected to counter the positive effect of the common elements as companies may de prioritise paediatric research and development. This may result in longer waiting times for children to get medicines adapted to their needs.

On **objective 4**, the reduction of administrative burden for all options analysed derive from the common elements (simplified and evolutionary PIP). In addition, for **Option A** the introduction of a supplementary reward in term of a voucher or of a supplementary extension of the SPC for UMN product may increase the overall administrative burden for companies and for public authorities. In the case of transferrable voucher, a system to manage the vouchers issues will need to be put in place and companies would be expected to fulfil further administrative requirements compared to the baseline situation. In the case of an extension of the SPC extension for products addressing UMN, in particular generic companies may face further complexity to plan the launch of generic medicines due to the further complexity that will be added to the SPC system.

Social impact: As mentioned in section 6.2.3, benefits for children derive from the avoidance of ADRs and increased quality of life thanks to medicines studied and authorised for specifically for them. However, as the average impact of ADR is relatively mild, even if potentially may result in a thalidomide-like scenario, and it is not possible to anticipate which products will be developed, it is not possible to provide a direct quantitative assessment of these benefits. The social impact is therefore related to the number of new paediatric products developed and to their timely access to patients due to a quicker completion of the necessary paediatric studies. The impact of the options

on the number of medicines for children has already been described under objective 1 above. Concerning the timely completion of PIPs both **Option A** and **Option C**, thanks to the common elements (cap of deferrals and simplification and streamlining of the PIP procedure) are expected to increase a faster completion of the PIP compared to the baseline, resulting to a quicker availability of products dedicated to children. In **Option B**, the removal of the reward for the completions of the PIPs, is expected to counter the positive effects of the common elements as certain companies my no more prioritise studies in children, resulting in later completion of the PIP and less products specifically developed for children.

7.2.2 Efficiency

Table 20 - Comparison of policy options in term of Efficiency – medicines for children

Criteria	**Baseline**	**Policy Option A**	**Policy Option B**	**Policy Option C**
Efficiency				
Overall costs and benefits	0	-	+	0
Administrative costs	0	-	+	+
Impact on SMEs	0	+	-	+

Estimated impact compared to the baseline: + + positive, + moderately positive, 0 neutral, – moderately negative, – – negative and – – strongly negative

Concerning saving and benefits, **Option A** gets the lowest scoring. The introduction of increased rewards for products addressing UMN of children would – on the one side - benefit economically the originator industry (441m gross benefit). On the other side, this would create also much higher costs compared to the baseline for health systems and patients (307 m). At the Opposite, **Option B,** abolishing the reward for the completion of PIPs is the one which is expected to score higher bringing benefits for patients and health systems (1510 m of savings) despite the higher costs for industry (in particular for originators -1756m) which will continue to be obliged to conduct PIP (even more than in the baseline due for example to the introduction of the mechanism of action in the common elements) without receiving any reward for this obligation. **Option C** for what concerns the saving and benefits originating from the paediatric SPC extension is expected to remain overall neutral compared to the baseline as the SPC paediatric extension will remain as in the baseline, the only difference in cost benefits for public authorities and industry will be related to the increased number of PIP and products that are expected to be developed as a consequence of the common elements.

Concerning administrative costs, the impact is expected to come from the common elements so all options are expected to score equality positive in this respect. Nevertheless, the novel rewards intended to be introduced under **Option A** are expected to increase the overall administrative costs for companies and for public authorities.

Concerning the impact on SMEs, **Option A and C** are expected to have a positive impact thanks to the common elements and the rewards granted for the conduction of paediatric studies. The abolition of the rewards on **option B** is expected to have a negative impact in particular on SMEs who may find more difficult to start paediatric development project due to abolishment of financial rewards for conducting clinical studies in children.

7.2.3 Coherence

Table 21 - Coherence

Criteria	**Baseline**	Policy Option A	Policy Option B	Policy Option C
Coherence	0	-	**-**	+

Estimated impact compared to the baseline + means that the assessment is positive, and – means that it is negative

In terms of *external* coherence the policy options have been assessed against the following initiatives: the SPC Regulation, the clinical trial Regulation, the HTA Regulation, national funding initiatives. Concerning the SPC Regulation, Option A and C, which maintain the SPC paediatric reward, are coherent with Regulation and its ongoing revision. The simplifications and reduction of administrative burden that the SPC revision will bring will be complementary to the ones that will be achieved by the simplification and streamlining of the PIP procedure. The **EU Clinical Trials Regulation**[199] facilitates the conduct of trials in small populations scattered in several MS. Therefore supporting measures of Option A and C in their intent to foster the development of new products in particular in areas of UMN. Option B, with the abolition of the SPC paediatric extension and the possible de prioritisation of clinical research in children by companies, may counter the positive effect expected from the clinical trial Regulation. The HTA Regulation, which is expected to overcome the national HTA procedures diversity, and to reduce their length and complexity in different Member States, is expected to be coherent with all the options

The coherence with the revision of the general pharmaceutical legislation has also been assessed. All the options proposed are coherent with the preferred option selected in the revision of the general pharmaceutical legislation and the two initiatives share similar objectives. In the case of transferable exclusivity vouchers (TEVs) foreseen in Option A, at first glance, there may seem to be incoherence between the two regimes. As in this impact assessment TEVs are considered as an ineffective incentive to generate innovation, whereas in the case of antimicrobials in the general pharmaceutical legislation, they may be a plausible incentive if applied strictly. This different conclusion stems from the 'special' character of the antimicrobial sector and the risk of a high number of TEVs if applied for paediatric medicines. The societal risk of AMR (which potentially concerns the whole population and not just a few patients) and its actual and potential economic consequences combined with the very limited development pipeline of antimicrobials suggests that the advantage of having TEVs specifically for novel antimicrobials may surpass the disadvantages of the high costs for the very limited number of TEVs that are likely to enter the market.

All policy options contribute to SDG 3 ("health/well-being") and SDG 9 ("innovation/infrastructure").

7.3 EU added value and proportionality and subsidiarity

All options for both initiatives bring EU added value for health systems/patients and pharmaceutical industry. All options for both initiatives are consistent with the EU's right to act under the Treaty of the Functioning of the EU (covering public health protection, the single market and the free movement of products within the EU). All options propose actions that will allow the objectives of the revision to be achieved to a greater extent than if Member States were acting alone. Furthermore, all options are proportionate in the sense that they do not go beyond what is necessary to achieve the objectives.

All options pursue the objectives of the revision and provide a clear demarcation between EU and Member State level actions. They do not propose any change to the national health care systems which are in the exclusive power of Member States (Article 168 TFEU), but the measures are expected to facilitate the development of medicines for rare diseases and children.

7.4 Limitations of the comparison

For both legislations quantification has not been possible for several indicators. Therefore qualitative analysis have been conducted. There is also a level of uncertainty in the findings described in this chapter owing to the influence of other contextual factors such as developments in the

[199] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC.

pharmaceutical sector, other relevant legislations (e.g. HTA Regulation, SPC Regulation) and policies at Member State level (e.g. for pricing and reimbursement). Further details are provided in Annex 4 section 3.c.

8 PREFERRED OPTION

8.1 Orphan medicinal products

The preferred option is **Option C**. This option is expected to provide a balanced positive outcome contributing to the achievement of the four objectives of the revision. It is expected to increase the number of orphan medicines compared to the baseline. It will especially refocus investments in products addressing HUMN, without undermining the development of medicines for rare diseases where treatments already exist but where new therapeutic options can still benefit patients and healthcare providers. This will boost research and innovation and would also improve the competitiveness of the EU industry including SMEs. Option C provides a balanced market exclusivity system, also allowing for earlier market entry of (similar) competitor orphan medicines while incentivising products in areas of HUMN. Options C leads to the best results in terms of patient access, due to the proposed access conditionality for the extension of the market exclusivity. The streamlining and the simplification of the procedures (better coordination between scientific committees, transferring the responsibility for orphan designation to the Agency) is expected to result in more efficient procedures and timely authorisation. Furthermore, more flexible criteria to better define an orphan condition will make the authorisation procedures more 'fit' to accommodate new technologies and reduce administrative burdens. The introduction of a Global Marketing Authorisation should also lead to a simplification of the system.

Table 22 - Yearly costs and benefit calculated per interested stakeholder group for preferred Option compared to the baseline

	Cost/benefit for **public payer and patients**	Cost/benefit for **originators**	Cost/benefit for **generic industry**
Option specific measures			
+1 year of ME for HUMN addressing medicines	+€82m additional cost 1-2 additional HUMN medicines per year	+€94m gross profit	- €13m gross profit
1 year of ME conditional for full EU launch	€288m cost saving from non-complying medicines (6 non-complying MP) Broader and faster access to complying medicines	-€282m gross profit loss (6 non-complying MP) +€4m additional cost (4 complying MP)	+€38m gross profit gain due to non-complying medicines (6 non-complying MP)
Common elements			
Day-1 entry of generic/biosimilars after ME expiry	€360m cost saving	-€354m gross profit loss	+€50m gross profit Predictable market entry
Abolishing 2-year ME extension for completing PIP	€96m cost saving legal clarity	-€94m gross profit loss	+€13m gross profit
Global marketing exclusivity	cost neutral, more predictable	Shorter protection time Stronger protection =cost neutral	cost neutral, more predictable
Total balance	**€662m cost saving** **+1-2 additional HUMN** **+9% broader and faster access**	**-€640m gross profit loss**	**+€88m gross profit**

The impact of preferred **Option C** will be complemented by elements of the preferred option and common elements in the revision of the *general* pharmaceutical legislation. In particular:

- The access conditionality, linking 1 year of additional regulatory data protection with effective placing on the market and supply of medicines in all Member States, within 2 years from authorisation, is aligned with the access conditionality of 1 year of additional market exclusivity for medicines for rare diseases. The positive effect on access and availability is expected to be even stronger for innovative and HUMN orphan medicines for which extended market exclusivity and regulatory data protection will be combined.
- Procedures will be simplified and streamlined. Provisions to streamline assessment activities between committees, and pre- and post-authorisation procedures, such as efficient interaction between different legal frameworks (e.g. medical devices) and downstream decision makers (HTA bodies, payers), abolishing renewals, integrating digital tools and real world evidence into the regulatory system and IT-driven processes (e.g. electronic submissions and variations of marketing authorisations) are some of the measures that are expected to reduce burdens and costs for companies and public authorities.

The legal instrument used is planned to continue to be a Regulation.

Competitiveness and future of innovation under reduced market exclusivity

Industry stakeholders claim that the reduction of market exclusivity period would harm future innovation and EU competitiveness. The incentives are agnostic to the geographic origin of the medicines, therefore the reduction would not harm EU companies more than non-EU companies coming to the European market (non-EU companies develop 80% of new medicines introduced to the EU market).

However, lower profits may transform into less innovation at a global scale. Option C estimates a total loss of €640m in gross profits. Industry re-invests on average 25% of their gross profit into R&D, consequently €160m may be lost for innovation. In 2021 the global pharmaceutical industry has invested €230b in R&D, hence the potential loss amounts to 0.07% of global R&D investment. If we wanted to translate this into medicines, only 1 in the next 1500 new medicines would not be developed because of the reduction, a likely invisible loss over the next 15 years.

Taken together with changes proposed in the general pharmaceutical legislation[200], and to the paediatric incentives, the combined effect remains marginal compared to global R&D investments.

8.2 Paediatric medicinal products

The preferred option resulting from the analysis presented in Chapter 7 is **Option C**. This option is expected provide a positive outcome contributing to all the objectives of the revision and results balanced under all the criteria screened.

Option C is expected to yield to an increased number of products in particular in areas of UMN needs of children which are expected to reach children faster than today while ensuring a fair return of investment for medicines developers who fulfil the legal obligation to study medicines in children, as well as reduced administrative costs linked to the procedures that follow from the obligation. The increased costs for public authorities and corresponding benefits for originators correspond to the expected development of more products addressing in particular UMN of children.

All stakeholder groups consulted support option C[201].

[200] The preferred option of the revision of the general pharmaceutical regulation has two variations, depending on the eventual length of the market launch incentive. One variation results in +€298m gross profit, and the other results in -€602m gross profit for the innovator industry.

	Cost/benefit for **public payer and patients**	Cost/benefit for **originators**	Cost/benefit for **generic industry**
Option specific measures			
Maintaining current extension	Cost neutral	Cost neutral	Cost neutral
Common elements			
Mechanism of action	3 more PIPs +€151m cost (1 SPC extension)	+€169m gross profit +€66m cost	-€33m gross profit
Cap in the maximum length of the deferrals	Faster completion of PIPs Cost neutral	Cost neutral	Cost neutral
Total balance	**+€151m cost** **+3 PIP** **+earlier access**	**+€103m gross profit**	**-€33m gross profit**

The positive impact of the preferred option will be complemented by some of the elements of the revision of the *general* pharmaceutical legislation. In particular

- The criteria to identify UMN to be defined in the general pharmaceutical legislation will be the same for medicines for children. Therefore medicines for children identified as addressing UMN will be entitled to any eventual additional regulatory incentives that could be granted to products addressing UMN. It is estimated that such provision will give an additional push to developers. Moreover, the additional regulatory incentives to be provided for products addressing UMN will serve as a "safety net" for a fair return on investment in cases when the SPC reward may not cover all Member States or may be not available (historically, around 50% of the completed PIPs benefitted from the SPC reward).
- Provisions linking regulatory data protection incentives with the effective placing on the market and supply of products medicines in all Member States, within a certain period of time, will also apply to medicines for children. This will further improve patient access to these medicines across the EU.
- Marketing authorisation procedures will be streamlined. This may decrease life-cycle costs for paediatric medicines and may help to ensure that originators maintain paediatric formulations over the entire life-cycle of the adult product and may increase the probability that generic companies copying the adult product will include the paediatric version[202].

The legal instrument used is planned to continue to be a Regulation.

8.3 REFIT (simplification and improved efficiency)

Preferred option orphans: The transfer of the responsibility for orphan designations from the Commission to the Agency is expected to result in simplification and increased efficiency. Furthermore, the abolishment of the yearly reporting for companies on the status of development of their orphan designation will entail less administrative burden. Better coordination between scientific committees will lead to faster assessment of the marketing authorisation application and lower the administrative burden for industry and reduce the number of interactions with the Agency.

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[201] In the public and targeted consultations, industry criticised the introduction of the mechanism of action as a common elements. However, they now support the measure as it brings alignment between the European and the US regulatory system: https://www.efpia.eu/about-medicines/development-of-medicines/regulations-safety-supply/stimulating-the-development-of-new-medicines-for-children/

[202] There is no obligation for generics and biosimilars to adapt their products to children friendly forms

Preferred option paediatrics: Streamlining and simplification of procedures for agreeing a PIP are expected to lower the administrative burden for industry. This is due to the reduced number of interactions with the Agency during the PIP process and to the simplified dossier that will be requited in certain cases. Industry strongly supports the simplification and streamlining of the PIP procedure.

8.4 Application of the 'one in, one out' approach

Orphan medicines: Reduction of the administrative costs for companies (about 3,6 m € per year) will result from preparing slightly fewer applications for an orphan designation and taking away annual reporting requirements. Pharmaceutical companies including SMEs, whose products are designated as orphan medicinal products, will continue to pay *reduced* fees for regulatory activities including for the marketing authorisation[203]. The implementation of the common elements will result in savings. Some of these savings will be offset by a slight increase in administrative costs for pharmaceutical industry due to the creation of a seven-year temporal validity for an orphan designation to stimulate timely product development and application for a marketing authorisation and the variable duration of market exclusivity for eligible products.

Paediatric medicines: A reduction of the administrative costs for companies per PIP will results from the simplification of the PIP procedure and from the new evolutionary PIP system. This streamlined process could affect up to 25-30 % of the procedures. There would be an increased effort for the Agency's Paediatric Committee (+ 10-20 %), but a reduced burden for industry (30%) due also to a better alignment with the US system.

Moreover, a less demanding PIP in the case of the paediatric only products will reduce burden and timing of the PIP preparation and application, including for PUMA products. However, specific impact figures cannot be provided as the number of paediatric only products cannot be anticipated.

An increase of the number of PIP and products is expected under the preferred Options and this has to be factored in the overall yearly administrative costs. The preferred option is therefore expected to result in a yearly reduction of administrative costs of 1,50 m €. Details are provided in Annex 3.

9 HOW WILL ACTUAL IMPACTS BE MONITORED AND EVALUATED

A series of monitoring parameters have been identified to evaluate the impact of the proposed measures on each of the objectives.

Table 23 - Proposed monitoring parameters

SPECIFIC OBJECTIVE	MEASURES OF SUCCESS AND RESPECTIVE MONITORING INDICATORS		DATA SOURCES
1. Promote innovation, in particular for unmet medical needs.	Pipeline of innovative new medicines for rare diseases and children.	• Number of orphan designations including for HUMN • Number of medicinal products for rare diseases and for children authorised • Number of medicinal products for rare diseases and for children authorised to address H/UMN of these populations • Number of PIP agreed on the base of the mechanism of action of the products • Number of PIP addressing UMN • number of pre-marketing regulatory support (scientific advice, PRIME, rolling review) • Number of research program financed by the EU concerning paediatric products addressing UMN	EMA data Data collected from EU research programs
Create a more balanced and competitive system	-Decreased costs for the healthcare	• Number of generic/biosimilar marketing authorisations.	OECD data; DG SANTE Country

[203] Orphan incentives | European Medicines Agency (europa.eu).

that keeps medicines affordable for health systems and patients while rewarding innovation.	system deriving from orphan products). -Faster introduction of generic and biosimilar medicines in Member States.	• Level of pharmaceutical spending per Member State for orphan medicines.	Health Profiles.
Ensure access to innovative and established medicines for patients.	-Timely access for medicines for rare diseases and children accessible in more Member States.	• Time to market in the various Member States of medicines for rare diseases • Time necessary for the completion of every PIP • Number of PIP finalised after the authorisation of the corresponding adult product and delay of the authorisation of the paediatric indication.	International HTA Database INAHTA, EMA data; IQVIA sales data; EMA data
Reduce the regulatory burden and provide a flexible regulatory framework.	-Reduction of approval time for orphan medicines. -Reduction of the time necessary to complete a PIP.	• Number of simplified PIPs agreed • Number of evolutionary PIPs agreed and conducted • Number of innovative study designs, orphan designations • Number of modifications per PIP • Average completion time of PIPs • Change in percentage of authorisation requests of orphan products granted	EMA data

All the data supporting the indicators are already collected at EMA level. They would not result in any additional administrative burden Annual reports on medicines for children are already published by the Commission could be adapted to accommodate the data mentioned above.

While some indicators (like the number of PIPs agreed or the number of orphan designated products) may provide some preliminary trends, only the number and type of medicines authorised will be able to provide a realistic picture if the objectives of the revision have been achieved. Therefore, it should be taken into account that the development of medicines is a long process and the completion of a clinical development plan can take up to 10-15 years. Incentives and rewards exert their effect up to 10 years after the marketing authorisation and the benefit for patients needs to be measured over a period of time of at least 5-10 years after a medicines is authorised.

ANNEX 1: PROCEDURAL INFORMATION

Lead DG, Decide Planning/CWP references

The Directorate for Health and Food Safety (DG SANTE) is the lead DG on the initiative on the Revision of the EU legislation on medicines for children and rare diseases.

The initiative is in the European Commission's Work Programme for 2022, in Annex II: REFIT initiatives, under the heading 'Promoting our European Way of Life'. The initiative has received the validation in the Agenda Planning on the 1 September 2020 (reference PLAN/2020/6688), and the Inception Impact Assessment was published on 24 November 2020.

Organisation and timing

An Inter-Service Steering Group was set up and included the Secretariat-General) Legal Service, BUDG (Budget), RTD (Research and Innovation), COMP (Competition), TRADE, GROW (Internal Market, Industry, Entrepreneurship and SMEs) and the JRC (Join Research Centre). It met 5 times from 30 October 2020 until 18 May 2022.

Consultation of the RSB

A first version of this Impact Assessment Report was submitted to the RSB on 30 May 2022, the meeting took place on 22 June 2022 and the RSB written (negative) opinion was received on 24 June 2022. After the first submission, the Board concluded the following:

1) The coherence and interaction with the general pharmaceutical legislation (and its revision) and other initiatives is not clear.
2) The presented narrative and intervention logic do not clearly describe and link the problems, objectives, proposed measures and their impacts, particularly in the area of availability and accessibility of these medicines.
3) The description and impact analysis of the options is unclear and their costs and benefits are neither well-presented nor compared. Given the apparent small differences between the impacts of the different options, the report does not sufficiently discuss the sensitivity of the impact analysis and how this uncertainty affects the conclusions.

The table below lists the changes in response to the recommendations of the RSB in its first opinion. Besides these modifications, targeted corrections and amendments have been included to address the technical comments provided by the RSB to DG SANTE.

Recommendation of the RSB	Modification in the impact assessment report in response to the Board's recommendations
(1) The report should clarify the links and overlaps with the general pharmaceutical legislation and its upcoming revision. It should be clear how the ambition of the general pharmaceutical legislation is included in this initiative and how the objectives and measures of the two initiatives create synergies and/or trade-offs. The link with other initiatives should be integrated better in the report, e.g. regarding cooperation at global level. Specific research programmes for these medicines and their link to the general development of medicines should be outlined. Based on a clearer problem identification, the report should present a more coherent narrative with clarified specific objectives and better linked measures. It should	Links with the general pharmaceutical legislation and explanations about the interplay have been included throughout the whole document. In particular, the intervention logic and Sections 5 (options) and 6 (impacts) have been amended. The options have been simplified (see also Annex 5 for a full overview of the options) in order to better allow their assessment and comparison and methodology has been aligned to better show the links with the revision of the general pharmaceutical legislation in order to be able to better take into account the impact of that revision on this SWD. This has allowed to better explain the ambitions of the initiatives, synergies and trade-offs that can be gained. Annex 8 has been introduced and further

better explain the enabling framework character of the initiative and that overall progress depends heavily on the effective interplay with other critical measures. This should help to better manage the expectations of the present initiative.	explains the overview of the overall legal pharmaceutical framework and related legal instruments like the SPC regulation. Relevant research programmes have been further outlined. Their link with the development of medicines has been further elaborated in Section 1.3.1 and Annex 8. The problem definition has been streamlined, a detailed problem tree has been added in the report. A full-fletched intervention logic has been added, better showing links between objectives and measures. The enabling framework character of both initiatives (general pharmaceutical revision and revision of the Regulations on medicines for rare diseases and children) have been made clearer, especially in Sections 1.3 and 2.1. The interplay with other critical measures, in particular those outside the competence of the EU and within the competences of Member States (pricing & reimbursement, for instance) has been further explained in Sections 2.1.2 and 2.1.3.
(2) The problems of availability and accessibility of these medicines should be clarified, together with their drivers, substantiated with robust evidence (e.g. EC pharmaceutical sector inquiry), and informed by the views of affected stakeholders. The report should be clear if the problems mainly lie with the Member States or the market behaviour of pharmaceutical industry or result from an economic market failure (e.g. lack of economic incentives). It should also be clear on the relative importance (and possible interaction) of the drivers and at which level these can be tackled most effectively while respecting subsidiarity and Member States competences. Finally, it should be clear what the different specific objectives are regarding availability and accessibility, how they relate to each other, and what the trade-offs are (e.g. higher absolute number of new medicines vs number of patients benefitting from new or less costly medicines).	The problems description has been clarified (see also point 1). The problems related to patient access have been further elaborated and substantiated in Sections 2.1 and 2.2 and have been informed by the views of affected stakeholders. It has also been made clearer what is in the EU's remit and what belongs to the Member States. It has been clarified how the different options and common elements aim to tackle issues concerning development on medicines and access to medicines by patients. The links between the specific objectives have been better outlined.
(3) The description of the options should be clarified, both in content and how the specific measures work together to tackle the problem drivers and reach the specific objectives. The effectiveness of the different measures in tackling the problem drivers and delivering on the specific objectives should be better assessed.	The options have been simplified and their functioning has been adjusted and clarified in Section 5. It has been further elaborated how the common elements work together with the options and how they aim to contribute to the achievement of the different objectives. It has also been assessed how the different policy

The report should clearly demonstrate that the proposed measures are complementary and compatible with the upcoming revision of the general pharmaceutical legislation.	options in tackling the problems and contributing to the achievement of the objectives including in relation to the pharmaceutical incentives under the general pharmaceutical legislation (in Sections 6 and 7). This to also calculate the cumulative effects of those two revisions. The complementarity of the two revisions has been demonstrated by reference to their common objectives (Section 2.2.) and by taking into account the impacts of the options of the general pharmaceutical legislation (Section 5).
(4) The analysis of the impacts should be structured better and presented clearly. The analysis should be understandable for a non-expert reader with cross references between results and calculations. The assumptions should be outlined clearly. The impacts on SMEs should be analysed further and the evidence available for assessing these impacts should be put forward. The report should be clear which measures are most cost-effective.	We have aligned the methodology used for the analysis of the assessment of the impacts (Section 6 and Annex 4) with the methodology used for the impact assessment of the *general* pharma legislation, with the aim to improve clarity, readability and consistency. The assumptions on which the model was based have been further explained and impacts on SMEs have been analysed, where possible. The available evidence on the impacts on SMEs has been presented in Section 6 and Annex 11 (SME test).
(5) The comparison of options should be supported by a clear overview of costs and benefits of the different options and a clear assessment in terms of effectiveness, efficiency and coherence. This should help the selection of a preferred option and in assessing its proportionality. The trade-offs for the different options regarding innovation, availability and affordability should be described, including possible unintended consequences such as earlier or later entering in the market of both innovative as well as generic medical products. Given the apparent small differences between the impacts of the different options, the report should better reflect the sensitivity of the impact analysis to the limitations of data and the modelling assumptions and how this uncertainty may affect the conclusions regarding the preferred options.	Chapter 7 has been improved to present independently and in a more extensive form the comparison of the options under the angles of effectiveness, efficiency and coherence. The trade-offs have also been described while comparing the options. The consequences (trade-offs) of the different options regarding innovation, patient access and affordability have been better described. The different options have been simplified and better described with a stronger focus on the monetary impacts per stakeholder with more significant results per option (avoiding small differences between the impacts).
(6) The report should present more systematically the views of different stakeholder categories on the problems, options and their impacts.	The views of different stakeholders have been systemically presented throughout the various Sections of the report.

A revised version of the Impact Assessment Report was submitted to the RSB on 28 October 2022 for a final opinion. The table below lists the changes in response to the recommendations of the RSB.

Recommendations of the RSB	**Modifications in the impact assessment report in response to these recommendations**
The report does not sufficiently assess the impacts of reduced regulatory protection periods on the sectors' capacity to finance future medicine innovation and international competitiveness.	A dedicated subsection on competitiveness and future innovation is added to section 8.1, on p. 67.
The report lacks clarity regarding safeguards for market access measures.	Section 5.2.1., description of policy options for rare diseases have been complemented, and explanation on the safeguards (and reference to the revision of the general pharmaceutical legislation) has been added to option C on page 32.
Some of the impact analyses are not sufficiently developed.	Several improvements have been introduced in the text: • Price differences and data accuracy – section 2.2.4 on p. 24 • A footnote explains the difference between scientific advice and Horizon Europe funding – section 5.2.2. p. 34 • An explanation on direct and indirect impacts of HUMN incentive is provided in Annex 4 (methodology) – section 3.d p. 104 • More details are added on how the percentage of population served over time is estimated for the options in Annex 4 (methodology) – section 6., p. 113 • An explanation on the concept of economic rent regarding the voucher is provided – section 6.1.1. p. 35 • Access gain is quantified in Figure 6 (p. 49) and Table 22 (p. 67)

Evidence, sources and quality

The Impact Assessment has built on the:

- Joint Evaluation of the Paediatric and Orphan Regulations (published in 2020)[204]

- Participatory workshops bringing stakeholders together to discuss various topics (see Annex 2: Stakeholder Consultation).

[204] https://ec.europa.eu/health/system/files/2020-08/orphan-regulation_eval_swd_2020-163_part-1_0.pdf

- The findings of the study on the economic impact of the supplementary protection certificates, pharmaceutical incentives and rewards in Europe[205].

Extensive stakeholder consultation was organised, with inputs gathered through a public consultation, targeted surveys, an interview programme and a focus group (for more information, see Annex 2: Stakeholder Consultation).

Evidence on costs of research and development was particularly difficult to gather. Public authorities and pharmaceutical companies provided only few responses to the costing survey. Data from published literature was also used.

[205] Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe (2018): https://ec.europa.eu/health/sites/health/files/human-use/docs/pharmaceuticals_incentives_study_en.pdf.

ANNEX 2: STAKEHOLDER CONSULTATION (SYNOPSIS REPORT)

a. Introduction

This report provides an overview of the consultation activities carried out in the context of the *Impact Assessment of the revision of the EU legislation on medicines for children and rare diseases*, the stakeholders and their opinions. These activities are:

- The public consultation (PC), from 7 May to 30 July 2021.
- Targeted surveys, including Options survey and Costing survey both for pharmaceutical companies and public authorities, from 21 June to 30 July 2021 (late responses were accepted until the end of September 2021, due to the summer period).
- Interview programme, at the end of June 2021.
- Focus groups, on 23 February 2022.

The following five key stakeholder groups (identified as priority groups by the EC) were targeted, namely:

1. Public authorities (European Medicines Agency (EMA), national competent authorities incl. ministries of health, health technology assessment (HTA) bodies, 'payers') in particular on topics such as rewards and incentives, regulatory procedures and efficiency, access, pricing and reimbursement.
2. Pharmaceutical companies (including small and medium-sized enterprises (SMEs)) in particular on their experience with paediatric investigation plans (PIPs), incentives and rewards, product development, as well as marketing authorisations.
3. Civil society representatives (e.g., patients, public health organisations) in particular on issues surrounding accessibility and availability, as well as unmet medical needs (UMN) and QALYs.
4. Healthcare providers (e.g., professional associations) in particular on the adoption of mechanism of action (MoA) criteria as well as questions relating to access and availability.
5. Academia/researchers/research organisations in particular on their involvement in clinical and pre-clinical research, scientific development, as well as the concerns linked to defining the current research priorities.

The consultation actions were agreed with the Inter-Service Steering Group in May and July 2021 and have been carried out as planned.

i. Public Consultation

The questionnaire of the PC[206], which was published on the Commission's *Have Your Say website*,[207] was made available in 23 official EU languages. A list of shortcomings identified in the Evaluation of the EU legislation on medicines for children and rare diseases was presented to the PC respondents. These included: (1) insufficient development in areas of the greatest needs for patients; (2) unequal availability, delayed access, and often unaffordable treatments for patients in the EU Member States (MS); (3) inadequate measures to adopt scientific and technological developments in

[206] Link to the OPC: https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12767-Revision-of-the-EU-legislation-on-medicines-for-children-and-rare-diseases/public-consultation_en.

[207] The published initiative 'Medicines for children & rare diseases – updated rules' on the Have your say website is available at https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12767-Medicines-for-children-&-rare-diseases-updated-rules_en .

the areas of paediatric and rare diseases and (4) procedures which are insufficient and burdensome. In view of this, citizens and stakeholders were invited to share their **views and experiences on the main obstacles** they face concerning treatments for rare diseases and children, on **possible ways to overcome** these obstacles, and **how to future proof the current legislation**.

In total, the PC received 305 responses, 87 of which came from non-governmental organisations, 67 from EU citizens, 39 from company/business organisations, 33 from academia/research institutions, 32 from business associations, 12 from public authorities, four from non-EU citizens, two from consumer organisations, and one from a trade union. As to the representation of SMEs, 12 stakeholders were micro, small and medium-sized companies/business organisations, from eight different Member States.

The remaining 28 responses have been submitted by 'other' stakeholder groups. Overall, 88.8 % of responses came from the EU MS, 3.6 from the US, while 7.8 % came from other countries.

In total, five separate contributions were submitted as part of the consultation activities. This includes position papers by APME (Association of Pharmaceutical Manufactures in Estonia) and Medicines for Europe, Novo Nordisk letter to the European Commission, and RECLIP's (Spanish Paediatric Clinical Trials Network) position on the proposed options.

It should be noted that multiple responses among different respondents that were either exactly the same or very similar were found. For instance, such responses were based on the official position of organisations such as EPFIA, EUCOPE and SIOPE.

ii. Targeted surveys

Options Survey

The Options Survey consisted of targeted questionnaires and was designed to engage with the EU-level and national public authorities, pharmaceutical industry representatives (including SMEs), civil society representatives (e.g., paediatric and rare disease patient organisations), healthcare providers and academia to gather detailed information on their views and preferences on the policy options as well as the costs of developing and marketing specific medicinal products.

In total, the Options Survey received 124 responses. Overall, public authorities were the most represented stakeholder group among the Options Survey respondents (46 %). Among public authorities, the representatives of EMA provided the most responses, followed by national agencies, the European Reference Networks (ERNs), health ministries, public health organisations, and national HTA agencies. Healthcare providers also provided a sizeable number (24 %) of responses. Among these were individual healthcare professionals, healthcare organisations, and one professional association. Academia was also relatively well-represented among the respondents (12 %). Fewer responses came from the pharmaceutical industry (9 %) and civil society (9 %).

Costing Surveys

Two types of Costing Surveys were designed: the *Costing survey for pharmaceutical companies* and the *Costing survey for public authorities*.

The **Costing Survey for pharmaceutical companies** consisted of a *questionnaire* to marketing authorisation holders of paediatric and orphan medicines. The questionnaires aimed at obtaining precise figures on administrative, research and development (R&D), manufacturing and marketing costs incurred specifically in relation to the development of paediatric and orphan medicines to inform the Cost-Benefit Analysis.

Only three responses were received to the Costing Survey from the pharmaceutical industry, namely three multinational pharmaceutical companies based in Europe or US. However, since none of them provided the requested cost elements, only a general qualitative description of the costs incurred, they were deemed insufficient for further analysis. Alternative strategies for the collection of relevant data have been identified, including through the analysis of the data from published

literature (mainly the SWD of the Joint Evaluation and Neez, et al. ("Estimated impact of EU Orphan Regulation on incentives for innovation." - Dolon Report 2020).

The **Costing Survey for public authorities** targeted the representatives of the national competent authorities and health ministries. The questionnaire was aimed at obtaining precise figures on the costs, including staff costs, costs of research subsidies distributed by national authorities, and costs of fee waivers and protocol assistance provided by the EMA. These data fed directly into the CBA.

Seven responses were received to the **Costing survey for public authorities**. These responses primarily contained quantitative information about the costs incurred by the same authorities; therefore, they fed directly into the CBA, and they will not be analysed in the Synopsis Report.

iii. Interview programme

The key goal of the interview programme was to collect in-depth information from the most relevant representatives from the five stakeholder groups on certain elements of different policy options as well as on their economic, social and environmental impacts.

60 interviews were conducted: the **majority (42 %) were with public authorities, 28 % were with the pharmaceutical industry, 13 % with academia, and 12 % with civil society representatives.** The least represented group, due to a low response rate, was the **healthcare providers making up 5 % of stakeholders** in the interview programme.

iv. Focus group

The purpose of the focus group dedicated to **potential changes in the current system of regulatory incentives foreseen under the Paediatric and Orphan Regulations** was to validate the key assumptions about the expected impact of a selection of changes. Five key stakeholder groups participated: civil society, healthcare providers, academia, pharmaceutical industry, and public authorities. The focus group hosted **78 participants**. The most represented groups among participants were **public authorities and civil society**, while a similar share of participants represented healthcare providers, academia and pharmaceutical industry[208]. In terms of public authorities, there were representatives from 17 different EEA countries[209].

Methodological approach

The relevant principles and steps on stakeholder consultations outlined in the Commission's *Better Regulation Guidelines* were followed in designing the consultation strategy. The stakeholder consultation's main steps included designing the consultation strategy, conducting consultation work, and informing policymaking through the preparation of the reports.

As with the PC, the data for targeted surveys was cleaned, where relevant, identical responses and campaigns were identified[210]. While for the targeted surveys, most questions helped to obtain quantitative data, the PC, interviews and focus group primarily gathered qualitative data.

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[208] The options given to the participants were: civil society, healthcare providers, academia, pharmaceutical industry, and public authorities. One participant did not identify with any of the five predefined stakeholder groups in the first Mentimeter question and was therefore named ‘unknown’ when responding to this and subsequent questions raised through this tool.

[209] Austria, Belgium, Cyprus, Croatia, Czech Republic, Finland, France, Germany, Ireland, Italy, Netherlands, Norway, Portugal, Romania, Slovenia, Spain and Sweden.

[210] https://ec.europa.eu/info/sites/default/files/br_toolbox_-_nov_2021_-_chapter_7.pdf.

b. Overview of results from the PC, surveys and interviews

General results

The consultation activities reaffirmed that the main problems affecting the two regulations are closely interconnected. For instance, primarily, the stakeholders highlighted concerns regarding the **insufficient economic interest** from companies and **limited funding for research**. While stakeholders expressed concerns about the **limited capacity of the regulatory framework** within the Paediatric Regulation to foster innovation, they agreed that *both* regulations present significant problems regarding a **lack of science in the definition of UMN**. Some stakeholders (in particular patients and academics) stated issues such as 'economic and operational difficulties', a high rate of waiver and/or deferrals, insufficient rewards and incentives, differences in rules across the EU, as well as limited access and availability of medicines which applied to *both* Regulations.

Paediatric Regulation

i. Paediatric investigation plan (PIP)

During the interview programme, stakeholders (in particular academics and industry) called for smoother and more efficient PIP procedures, better coordination of the committees (particularly highlighted by the pharmaceutical industry) and faster opinion delivery. Regarding the latter point, the stakeholders from the pharmaceutical industry and academia emphasised that while the opinion on a PIP can be delivered in 60 days, in practice, most PIPs are delivered in 120 days.

With regards to the ***deferrals***, results from the interview programme revealed that deferrals were considered needed for ethical reasons, trial recruitment and formulation issues, and for finalisation of toxicological evaluations, as noted by the pharmaceutical industry, public authorities and academia. Some interviewed representatives from public authorities and academia mentioned ways to possibly reduce deferrals. The suggestions included transferable vouchers, tax credits and other factors outside the Paediatric Regulation (improvement of trial preparedness, standardisation of health data and health data records to provide evidence).

ii. Unmet Medical Needs (UMN)

With regard to UMN, the targeted surveys and interviews covered the following subtopics: (1) criteria for UMN, (2) systems to identify UMN, (3) measures to develop medicines for UMN, (4) research and development support to UMN, and (5) novel rewards for products addressing UMN. At the same time, the OPC consulted stakeholders on subtopics (1), (3), and (4). Overall, stakeholders continue to consider UMN a serious issue within the Paediatric Regulation.

With regards to the ***criteria*** to define UMN, **around 80 %** of *all stakeholder groups* participating in the Option Surveys indicated that the **'seriousness of the disease'** and **'no authorised treatment for the disease available'** should be included among the most relevant criteria for defining paediatric UMN, while interviewees and OPC respondents generally considered all criteria[211] important when defining paediatric UMNs. Some interviewees cautioned *'not to define it too narrowly through a legislation'*; other interviewees explained that there is a need for a flexible framework to identify UMN. Importantly, the issue of **appropriate formulation** of products was raised by several interviewees.

[211] Seriousness of the disease (life-threatening and/or seriously debilitating and/or chronically and progressively leading to a seriously debilitating status). No authorised treatment for the disease is available (therefore, a clear need for any treatment for a disease), and no commonly used method that would not be subject to marketing authorisation is widely available (e.g., surgery). Treatments are already available, but the corresponding therapeutic efficacy and/or the safety would need to be significantly ameliorated. Treatments impose an elevated treatment burden for patients. Available treatments are not addressing unmet medical needs in all paediatric ages (e.g., adapted doses and / or formulations / routes of administrations specific to neonates).

With regard to the systems to identify UMN, the general attitudes revolve around UMN being **difficult to define** (particularly among industry and academia) and that this ought to be done in a **multi-stakeholder approach**. Furthermore, the public authorities consulted in the Options Survey provided some suggestions on mechanisms to *better* identify paediatric UMN: **modifying the system of incentives**, **expanding and better monitoring the off-label use of medicines for children**, and **directly engaging with patient representatives and healthcare providers**.

In the Options Survey, the respondents stated that there is a **need to revise a rewards and incentives system**, create **research-driven funds**, and **modify a waiver system**. In addition, a need to introduce a **possibility to link the six-month Supplementary Protection Certificate (SPC) extension** to the timely completion of a PIP and/or the extension by two years of the market exclusivity for paediatric medicines is not an alternative to the six-month SPC extension was noted.

i. Mechanism of Action criteria

During the consultation activities, various stakeholder groups emphasised the need for paediatric drug development to be driven by the mechanism of action (MoA) via a revision of the conditions for granting a waiver. Such a system was supported by academia (91% of correspondents), civil society (86% in favour), public authorities (84 % in favour), and healthcare providers (80 % in favour), but there was little or no support from the pharmaceutical industry[212]. Multi-stakeholder discussions should be arranged in order to introduce further changes and strategies. With regards to the therapeutic area, the majority of interviewees were sceptical of going outside oncology. The main concerns related with the need for an adequate level of understanding in biology, the need for considering diseases with the same genetic cause and the difficulty of obtaining reproducible data. Only some public authorities considered this possible.

ii. Rewards and incentives

Stakeholders consulted via the OPC, targeted surveys, and interviews considered an **insufficient reward and incentives system** as one of the main problems affecting the development of paediatric medicines for UMN. In the Option Survey, respondents from academia and the pharmaceutical industry argued that a **novel complementary reward should be introduced and/or the existing rewards and incentives should be modified** to make them more effective, proportionate, and flexible in addressing the market failure in both paediatric and orphan regulatory areas.

Stakeholders who provided responses to the Option Survey suggested that these complementary actions could include **modifications in the pricing policy**, which, in their view, should aim to assign economic value to any new paediatric indication derived by new clinical research as well as **innovation and investment in off-patent paediatric developments.** Within OPC, stakeholders suggested designing new solutions based on case studies on how antimicrobial resistance (AMR) research and development are incentivised and expeditated, for instance, through pull incentives as well as establishing negative incentives for companies (under revocation of patent protection) if they do not implement these voluntarily. Further complementary actions, such as early rewards or sharing of the resulting data, were also mentioned.

iii. Research priorities

In the Option Survey, nearly half of the respondents from academia (41 %) stated that the **EC should set future research priorities**, whereas slightly more than a third of the respondents (35 %) thought that they should be set by national health agencies and public authorities.

Some interviewees from public authorities observed that the issue with research, in general, is neither funding nor setting the right research priorities, but rather '*a failure of the demand'*, linked to

[212] Only one response from the pharmaceutical industry was recorded.

failures in clinical research and the issue of a small market. Therefore, improvements to clinical trials and pre-commercial procurement could be useful to address the research and development in specific areas.

iv. Access and availability

In the Option Survey, 60 % of the respondents from civil society and healthcare providers stated that accessibility to paediatric medicines had improved somewhat in recent years[213]. Approximately 23 % of respondents, all from the healthcare providers group, also emphasised that the COVID-19 pandemic affected access to paediatric medicines.

During the Option Survey, stakeholder groups also outlined the main ***barriers*** to the accessibility of paediatric medicines: insufficient public/private investment in research and development for paediatric medicines (25 % of respondents) and strategic commercial decisions by companies (25 % of respondents), followed by national pricing and reimbursement policies (21 %), national drug pricing policies (16 %), and EU-level market authorisation procedures (9 %). Some respondents from the healthcare providers group also outlined that the national procedures for marketing new medicines are taking too much time. Other issues emphasised during the OPC and interview programme by civil society and the EU citizens included lack of access to essential medicines due to shortages, lack of child-friendly formulations, and lack of financial access for newer medicines in some EU countries.

v. COVID-19 impact on paediatric medicines

In the Options Survey, nearly half of respondents (44 %) from all stakeholder groups answered that they encountered **problems affecting paediatric research activities due to the impact of COVID-19**. The impact was most evident as implementation of clinical trials has been paused while the research funding has been reduced. Additional restrictions were further imposed, such as patients' access to hospitals and healthcare services, labs, and face-to-face events. Although only 12 % of the respondents in the Option Survey stated that the pandemic was affecting access to paediatric medicines, during interviews, stakeholders from civil society emphasised that the COVID-19 pandemic had exacerbated the shortage of paediatric medicines and increased the risks of under-cured paediatric patients affected by COVID-19 and its complications.

[213] 32 % of respondents from healthcare providers group emphasised that, in recent years, accessibility had not improved at all or had remained the same.

Orphan Regulation

i. Orphan designation criteria

In general, stakeholders from the pharmaceutical industry emphasised that the **current orphan designation criteria are predictable** and **have been effective** in encouraging the development of products for rare diseases. With regards to the ***prevalence threshold***, a clear message from the consultation programme was that lowering the prevalence threshold would not address UMNs better. As interviewees underlined, products for some rarer diseases (with a low prevalence) are available and while there are none for some more widespread diseases.

With regards to the use of the ***incidence criteria*** for rare cancers and short duration diseases to help focus the development of orphan medicines in areas of UMN, some stakeholders supported the implementation of such criteria; others regarded it as *challenging*. In the Options Survey, slightly more respondents agreed than disagreed with this change (28 % and 25 %, respectively). At the same time, during the interview programme, representatives from academia agreed on the incidence criteria for rare paediatric cancers, and some interviewees from civil society suggested the 'combined use' of both prevalence and incidence to define rare diseases.

With regards to the introduction of a ***cumulative prevalence*** criterion for products with more than one orphan designation, the participants in the consultation programme provided varying views. For example, a new criterion of cumulative prevalence was endorsed by a share of academia and public authority representatives, while other stakeholders from the pharmaceutical industry did not support it. According to the pharmaceutical industry representatives, this was mostly because the developments in more orphan indications and prevalence should not be penalised. They also recognised that the fact that an orphan medicinal product is useful for more than one condition (as happens for cancers) is overall a positive aspect, rather than something to be penalised.

A point that stood out during the interviews was that **the prevalence or incidence criteria for cancers**, according to academia, should *still* define a rare population in the Regulation (including for the tissue-agnostic medicines). Furthermore, representatives from academia suggested the **use of ROI as a criterion in addition to prevalence** (or incidence) and *not* alternatively to prevalence. According to the stakeholder, this would avoid overcompensation. At the same time, public authority representatives suggested considering a threshold (without specifying which one) to possibly prolong the market exclusivity period.

ii. Significant benefit

With regards to ***significant benefit***, different stances were expressed by stakeholders**.** In the Options Survey, the majority of stakeholders from *all* groups (48 %) agreed that **the current rules for demonstrating significant benefit should be modified** to ensure that products provide real benefit**.** Public authorities highlighted that significant benefit should be tightened up and evaluated more strictly, for instance, by requiring proof of clinically relevant effect. Moreover, during the interview programme, public authorities recognised that such rules could be improved as sometimes they are difficult, particularly at the time of marketing authorisation when more robust data are needed, especially in areas such as the following: (i) 'Crowded' areas where there are other treatments available, (ii) Oncology where there are first- or second-line treatments, (iii) Combination therapies, (iv) New formulations that are less convenient for patients, (v) When efficacy and safety could not be compared as at the time of marketing authorisation application, data could be limited, and therefore, it is difficult (and unfair) to compare this limited data with the safety data of another product already on the market for many years, (vi) When the demonstration of significant benefit is based on 'major contribution to patient care'. This sometimes means that previous / available medications may 'harm' patients. In this assessment, it is important to hear the opinion of the patients.

iii. Unmet medical needs (UMN)

With regard to UMN, the targeted surveys and interviews covered the following subtopics: (1) criteria for UMN, (2) systems to identify UMN, (3) measures to develop medicines for UMN, (4) research and development support to UMN, and (6) novel rewards for products addressing UMN. At the same time, the OPC consulted stakeholders on subtopics (1), (3), and (4).

With regards to ***criteria*** to define UMN, many stakeholders participating in the consultation activities confirmed that all proposed criteria are essential. In the Options Survey, the most relevant criteria for defining UMN were **the seriousness of the disease**, **no authorised treatment for the disease is available**, and **no commonly used method that would not be subject to marketing authorisation is widely available**. The pharmaceutical industry suggested that **the ROI criteria can be elaborated further**, and there is a need for **clear guidance on indications and scenarios**. Furthermore, during the interviews, the pharmaceutical industry and civil society considered quality of life as an additional criterion to define UMN.

With regards to the ***systems to identify*** UMN, stakeholders participating in the consultation programme, including the pharmaceutical industry, academia and civil society, tended to agree that the definition of UMN in rare diseases should be **dynamic** and supported the idea of introducing a multi-stakeholder dialogue at a very early stage of the development since the definition varies in content and across different stakeholder groups.

In the Option Survey, three ways to identify unmet needs were proposed[214]. All of the stakeholder groups except for the pharmaceutical industry (45 % of respondents in total) identified ***criteria*** **defining UMN in rare diseases should be established in the EU legislation and detailed in scientific guidelines**, which could be updated regularly as the most appropriate. Public authorities participating in the interview programme specified that such criteria would facilitate work or regulators and make its [*work*] more predictable.

With regards to the **creation of *a list* of UMN**, the conclusion was that the majority of stakeholders see it as *unfeasible*. Civil society specified that such a list could be only valuable for research, while public authorities propose that **a list of 'crowded areas'** would be an easier and more effective option.

iv. Rewards and incentives

Similar to the development and regulation of paediatric medicines, **insufficient rewards and incentives** were outlined as one of the key barriers to developing orphan medicines by most stakeholder groups and pharmaceutical industry in particular during the consultation activities of the OPC, targeted surveys and interviews. All stakeholder groups agreed that the **revision of the current reward and incentives system is needed**.

To revise the current system, respondents from civil society emphasised that the **one-size-fits-all incentive framework is not sustainable** for national healthcare systems. Thus, rewards and incentives should be differentiated**.**

v. Research priorities

Similar to the paediatric Options Survey results, nearly half of the respondents (44 %) from academia, the pharmaceutical industry and public authorities thought that the **EC should be responsible for setting the research priorities**. However, around a third of respondents (31 %) stated that others should be responsible for this task. A frequent suggestion was to involve all

[214] A list of UMN in the areas of orphan medicines in the EU legislation and updated regularly; A definition of UMN in rare diseases in the EU legislation; Criteria defining UMN in rare diseases in the EU legislation and detailed in scientific guidelines, and updated regularly.

stakeholder groups in the process. Likewise, the interviewees from the pharmaceutical industry sustained a '*more integrated approach for fostering research and development'*, as well as an '*ecosystem*' that drives the '*basic research'* and '*transnational research'*. In this context, according to the interviewees, this '*ecosystem*' could be complemented with an '*additional incentive such as a transferrable exclusivity extension, but only in the context of a broad ecosystem*.'

vi. Scientific developments

During the interview programme, the stakeholders were asked to suggest elements to define 'innovative products'. Some suggestions were provided, including: high therapeutic value, new target (new knowledge about the disease), the product itself (e.g. combinations of antibodies, construct which has several elements), delivery (a new and different way to deliver the medicine) and cure versus care.

When asked whether **orphan designation should <u>not</u> be granted to subsets of common diseases** to avoid unnecessary multiplications of rare diseases out of common diseases, the majority of the Options Survey respondents (76 %) from academia and public authorities' groups agreed with this approach.

During the interview programme, it became clear that **a novel scientific-based approach should be used** to define an orphan condition. However, both public authority and industry interviewees recognised that innovation should also be considered outside the Orphan Regulation, and this should include how to get scientific advice early in the development, how to support trial designs in a better way, how to get evidence from Real World Data (RWD), the role of the regulation in innovation, better capacity building and coordination of expertise at EMA level. Finally, industry representatives deemed there is no need for additional measures for similarity assessment for ATMPs.

vii. Efficient procedures

Around 65 % of Options Survey respondents from academia, the pharmaceutical industry and public authorities supported **transferring the responsibility for identifying medicines for use against a rare disease from the EC to the EMA[215].** Some stakeholders who opposed this change[216] stated that they were *satisfied* with the current system. Around half of respondents agreed that this change would result in decreased administrative burden and more efficient procedures, and around a quarter of respondents said it would *not* make a difference. During the interview programme, public authorities assumed that such a transfer of responsibility would not be revolutionary for the *outcomes* of assessments, as there are very few examples when the COMP opinion is not taken over by the EC.

One of the key takeaways from the interview programme in regard to this topic was that the streamlining of procedures is *not* a matter of changes to the Orphan Regulation, but rather, it is a matter of the general regulatory system as a whole (i.e. this should be addressed within the Pharmaceutical Strategy).

viii. Access and availability

The Options Survey results revealed that more than half of the respondents from healthcare providers and civil society groups (63 %) regarded **the accessibility at least as somewhat improved** since 2017. Concerning the barriers that limit access and availability of orphan medicines, healthcare providers and civil society named **insufficient research and development** (28 %) and **strategic commercial decisions by companies** (20 %), followed by the **national pricing and reimbursement policies** (16 %), **companies' strategic (launch) decisions** (16 %), **national regulations** (14 %), and **EU-level procedures** (4 %).

[215] With 16 % expressing strong support.
[216] 14 % of the public authority and 22 % of the pharmaceutical respondents.

With regard to potential solutions, the majority of respondents (78 %) and particularly from academia, healthcare providers and public authorities' groups, suggested in the Options Survey encouraging **companies that lose commercial interest in a medicine to offer it for transfer to another company**. However, during the OPC, stakeholders from the pharmaceutical industry emphasised that companies already engage in licensing deals and transfer their products to another company when there is a shared interest on both sides. Respondents to the survey (68 %) also agreed with **fostering competition from generic and biosimilar medicines by ensuring these medicinal products can enter the market a day after the expiry of the exclusivity period**. This was mainly supported by respondents from the academia, healthcare providers and public authorities' groups. However, it should be noted that during the interviews programme, companies (excluding generic companies) did not consider the increase of generic competition as one of the main concerns relating to the development of orphan medicinal products.

The option to introduce **a limit on the validity of an orphan designation to encourage timely medicine development** gained support from a little less than half of the respondents (48 %), mainly from the academia and healthcare providers groups participating in the Option Survey. All stakeholder groups supported the **harmonisation of procedures on the EU-level** regarding orphan medicines development as raised in all the consultation activities.

ix. COVID-19 impact on orphan medicines

Based on the Options Survey responses, most respondents (39 %) stated that they experienced no problems relating to orphan medicines caused specifically by the COVID-19 pandemic. There were some stakeholder groups that did not know / could not answer this question (29 % of respondents from academia and 21 % of respondents from public authorities). This could be due to the fact that the pandemic is ongoing, and the exact impact cannot be quantified just yet. However, a large proportion of healthcare providers (50 %) thought that the pandemic is affecting **access to orphan medicines**, while 18 % of the public authority respondents stated that COVID-19 is affecting **research activities** relating to rare diseases.

In addition to the negative consequences of the pandemic, many stakeholders highlighted '*lessons learned*' and positive takeaways that could be adapted for the future of orphan medicine development. For instance, the interviewees from the pharmaceutical industry noted that **fostering the utilisation of digital tools** and **telemedicine** could be welcome integrations into the day-to-day practice. However, this would necessitate additional resources for public authorities.

c. Overview of results from the focus group

The focus group discussion was structured around the results of the interactive assessment of **six key questions** focusing on the expected impacts of a selection of changes proposed for the current system of regulatory incentives foreseen under the Paediatric and Orphan Regulations.

On the impact on paediatric products, if the 6-month SPC extension was reduced or abolished, respondents were rather divided among those expecting a proportional decrease in the number of all PIPs and paediatrics products (40%) and those who expected no change (36%). The question was linked to the obligation of completing the PIP. The representatives of national public authorities argued that the **current 6-month SPC extension does not take into account cases when the development of a product takes longer**. Despite the frequency of these cases, the obligation remains the same.

Moreover, **the risk of losing the SPC extension seems not to be enough to accelerate the PIP completion (**32 % of the participants agreed, 46% of participants **did not know or thought that this question was not relevant for them** while the smallest but still significant share of participants (22%) disagreed). Difficulties in recruitment and the complexity of PIPs were mentioned as the main obstacles in the completion of PIPs by industry.

Regarding the impact on products addressing unmet need, if the 10 market exclusivity was reduced or abolished, most participants who responded to this question (62%) expected a **proportional decrease in the number of orphan designations and products**. The need to **review and discuss the possibility to revoke certain incentives granted to the manufacturers** under the current legislation if their impact proves inadequate was recognised, while making the distinction between reduction of incentives and their abolishment. Finally, the representatives of public authorities also highlighted that the current Orphan Regulation **enables repurposing of medicines and many of these medicines are not covered by any patents**. Given this, it is particularly important to consider the intersection between paediatric and orphan products.

Nearly half of the participants in the focus group agreed that the risk of receiving a reduced ME incentive would improve the availability of products actor Member States. However, the decisions related to the availability are not fully in the hands of the marketing authorisation holders. In addition, limiting incentives to products addressing areas of unmet needs was not recognised by all as a way to shift the investments of the industry to those areas: on the one hand, over half of the participants who responded to this question (51%) **disagreed** with the assumption that **limiting incentives to products addressing areas of unmet needs would shift the investments of the industry to those areas**. On the other hand, over a third of respondents (37%) agreed that limiting incentives to products addressing areas of unmet needs would shift the investments of the industry to those areas for both paediatric and orphan products.

Finally, participants were asked to identify which of the proposed solutions regarding the support for the development of products in areas of unmet needs they most agreed with. Most respondents (40%) stated that **no new reward or incentive was needed to support the development of products in areas of unmet needs**. In terms of two different types of vouchers proposed, more respondents supported the introduction of transferable regulatory vouchers (36%) over transferable priority review vouchers (24%). It was also noted that the option involving both vouchers might have been selected by some participants if it was presented among the pre-defined options.

Stakeholders generally agreed that the key issue in the current Paediatric and Orphan Regulations is that the existing measures **do currently incentivise the timely evaluation and development of medicines**. Most agreed that the focus should be on creating a **system that can sustain the existing pathways**, **with some additional measures targeting unmet needs**.

Summary of the focus group discussion

All in all, a need for a holistic approach to the revision of the EU legislation on medicines for children and medicines for rare diseases emerged. There is a need to direct more EU and national research funding to the start-up level to simulate the development of new products and their reimbursement, and make sure they reach patients. Most stakeholders agreed that the current system of incentives and rewards should not be abolished or reduced but rather adapted to the evolving priorities and better tailored with additional conditionality. The introduction of transferable regulatory vouchers has received greater support when compared to transferable priority review vouchers. However, the experience concerning these proposed types of vouchers within the regulatory system remains limited; therefore, a lot of questions concerning the risks of overcompensation, exploitation, unpredictability and time constraints have been raised. Thus, in revising the system, stakeholders asked to dedicate a particular attention to mitigating the risk that new incentives could potentially skew competition or result in other unintended consequences. Finally, given the close links between the revision of the Paediatric and Orphan Regulations and the revision of the General Pharmaceutical legislation, which is being carried out in parallel, all stakeholder groups agreed with the need for further consultations in the upcoming year.

ANNEX 3: WHO IS AFFECTED AND HOW?

1. Practical implications of the initiative

For the Orphan Regulation

The planned revision of the legislative framework on medicines for rare diseases is expected to have an impact on patients, payers/health systems and pharmaceutical companies.

Concerning **patients**, benefits derive from more orphan medicinal products accessible in particular in areas of HUMN.

Originators will benefit from simplified procedures with the Agency and more gross profit from the sales of (HUMN) orphan medicinal products developed. Costs mainly relate to gross profit loss due to the access conditionality and faster entry of generics/biosimilars after the expiry of the market exclusivity. In particular, SMEs will benefit considerably from the simplified procedures.

The legislation will result both in costs for payers/**health systems** (due to the extra year of market exclusivity for HUMN) and in benefits (mainly cost savings of the 1-year of market exclusivity conditionality for non-complying medicines; faster entry of generics/biosimilars).

For the Paediatric Regulation

The planned revision of the legislative framework on medicines for children is expected to have an impact on pharmaceutical industry, health systems/public authorities and patients.

Concerning **patients**, benefits derive from the study in children and of new medicines in particular in areas of UMN resulting (thanks for example to the introduction of the mechanism of action provision) in the avoidance of ADRs and increased quality of life thanks to medicines studied and authorised for children. As explained in section 6 very serious ADR due to the off label use of a product are very rare event and cannot be captured with historical data. While the average impact of ADR could relatively mild, a single very rare case of serious ADR would have the potential to create a thalidomide-like scenario. In addition, specifically researched medicines for use in children may result in breakthrough treatments for diseases for which no treatment at all was available, thereby increasing considerably the quality of life of the affected children, beyond the avoidance of ADRs. As it is not possible to anticipate which products will be developed is not possible to provide a quantitative assessment of this effect. Patient are also expected to benefit a faster access to medicines thanks to a faster completion of the PIPs due to the simplification of the PIP procedure and to the cap of the length of the deferrals.

Pharmaceutical industry are expected to develop more products in areas of UMN for children and at the same time benefit from simplified procedures for agreeing with the Agency on the paediatric development plans which they will have to conduct leading to a reduction of their administrative costs per product developed. .

The legislation will mainly results in direct costs for **public authorities** will mainly due to the costs resulting from the rewards that will be allocated to the products developed thanks to the legislation. However, it should be considered that more products for children are expected to consist in savings from avoided hospitalisation and avoided outpatient treatments. Such benefits were calculated in the Joint Evaluation on the basis of products developed and resulted in minor, almost irrelevant impacts and therefore have not been quantified in this SWD, however, as explained above, the use of non-properly tested product in children may result in catastrophic consequences and in a thalidomide like scenario.

2. Summary of costs and benefits

For the Orphan Regulation

I. Overview of yearly Benefits (compared to baseline benefits – million €) – Preferred Option

Description	*Amount*	*Comments*
Direct benefits		
Pharmaceutical companies (originators)	+€94m gross profit due to +1 year of ME for HUMN medicines	
Pharmaceutical companies (generic industry)	+€38m gross profit gain due to non-complying medicines on launch conditionality +€50m gross profit due to predictable market entry ('day-1') +€13m gross profit due to abolishing 2-year ME for completing PIP	
Public payer/health systems and patients	+€288m cost saving from non-complying medicines access conditionality and broader and faster access to complying medicines +€360m cost saving due to predictable market entry ('day-1') +€96m cost saving legal clarity abolishing 2-year ME for completing PIP	
Indirect benefits		
Administrative cost savings related to the 'one in, one out' approach*		
Direct administrative costs savings	**4.5 m** €	Direct cost saving

*Estimates are gross values relative to the baseline for the preferred option as a whole (i.e. the impact of individual actions/obligations of the preferred option are aggregated together); (2) Please indicate which stakeholder group is the main recipient of the benefit in the comment section;(3) For reductions in regulatory costs, please describe details as to how the saving arises (e.g. reductions in adjustment costs, administrative costs, regulatory charges, enforcement costs, etc.;); (4) Cost savings related to the 'one in, one out' approach are detailed in Tool #58 and #59 of the 'better regulation' toolbox. * if relevant*

II. Overview of costs – Preferred option							
		Citizens/Consumers		**Businesses**		**Administrations**	
		One-off	**Recurrent**	**One-off**	**Recurrent**	**One-off**	**Recurrent**
Costs for +1 year of ME for HUMN products	Direct costs				13 m € loss in gross profits (generic industry)		82 m € additional costs

Costs for 1 year of ME condition for full EU launch	Direct costs				282 m € loss in gross profits (originators) 4 m € additional costs		
Costs Day-1 entry of generic/biosimilars after ME expiry	Direct costs				354 m € loss in gross profits (originators)		
Costs Abolishing 2-year ME extension for completing PIP	Direct costs				94 m € loss in gross profits (originators)		
Administrative costs due to increased number of orphan designations					1.3 m €		
Costs related to the 'one in, one out' approach							
Total	Direct adjustment costs	N.A	N.A	N.A	N.A		
	Indirect adjustment costs	N.A	N.A	N.A	N.A		
	Administrative costs (for offsetting)	N.A	N.A	N.A	**1.3 m** €		

(1) Estimates (gross values) to be provided with respect to the baseline; (2) costs are provided for each identifiable action/obligation of the preferred option otherwise for all retained options when no preferred option is specified; (3) If relevant and available, please present information on costs according to the standard typology of costs (adjustment costs, administrative costs, regulatory charges, enforcement costs, indirect costs;). (4) Administrative costs for offsetting as explained in Tool #58 and #59 of the 'better regulation' toolbox. The total adjustment costs should equal the sum of the adjustment costs presented in the upper part of the table (whenever they are quantifiable and/or can be monetised). Measures taken with a view to compensate adjustment costs to the greatest extent possible are presented in the section of the impact assessment report presenting the preferred option.

For the Paediatric Regulation

The figures cited in the tables below illustrate the benefits and the costs under the preferred options in relation for the affected stakeholders. They are based on the assessment of costs and benefits described in Section 6.2 and Annex 4 section 7.

The figures are presented in comparison with the baseline and are average annual costs in m€

I. Overview of benefits (compared with baseline costs) – Preferred Option. Yearly costs		
Description	***Amount***	***Comments***
Direct benefits		
Industry, originators	169 m gross benefit	Benefits deriving from one estimated SPC extension per year
Patients	3 extra PIPs for products addressing UMN of children Faster completion of PIPs and consequently medicines reaching faster children	Not possible to determine the benefits as it will depend greatly from the products that will be developed
Administrative cost savings related to the 'one in, one out' approach*		
Direct Administrative costs savings	**2.8 m**	Administrative savings for companies deriving from the simplification and streamlining of the PIP procedures

II. Overview of costs (compared with baseline costs) – Preferred option							
		Citizens/Consumers		**Businesses**		**Administrations**	
		One-off	**Recurrent**	**One-off**	**Recurrent**	**One-off**	**Recurrent**
Costs for conducting extra PIPs for originators	Direct costs				66 m €		
Cost for delayed generic entry due to one extra SPC paediatric extension granted per year					33 m €		
Costs for public authorities due to the extra SPC paediatric extension granted					1.3 m €		76 m €
Costs for patients			75 m €				

due to the extra SPC paediatric extension granted leading to delayed entry							
Administrative costs due to increased number of PIP conducted					1.3 m €		
Costs related to the 'one in, one out' approach							
Total	Direct adjustment costs	N.A	N.A	N.A	N.A		
	Indirect adjustment costs	N.A	N.A	N.A	N.A		
	Administrative costs (for offsetting)	N.A	N.A	N.A	1.3 m €		

3. Relevant sustainable development goals

III. Overview of relevant Sustainable Development Goals – Preferred Option(s)		
Relevant SDG	**Expected progress towards the Goal**	**Comments**
SDG no. 3 – Good health and wellbeing	Support the research and development of vaccines and medicines for the communicable and non-communicable diseases that primarily affect developing countries, provide access to affordable essential medicines and vaccines, in accordance with the Doha Declaration on the TRIPS Agreement and Public Health, which affirms the right of developing countries to use to the full the provisions in the Agreement on Trade Related Aspects of Intellectual Property Rights regarding flexibilities to protect public health, and, in particular, provide access to medicines for all	
	Strengthen the capacity of all countries, in particular developing countries, for early warning, risk reduction and management of national and global health risks.	
	Achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential	Increase of medicines especially in areas of HUMN and paediatric medicines

	medicines and vaccines for all.	
	By 2030, reduce by one third premature mortality from non- communicable diseases through prevention and treatment and promote mental health and well-being.	
	By 2030, end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases.	
SDG no. 9 – industry, innovation and infrastructure	Enhance scientific research, upgrade the technological capabilities of industrial sectors in all countries, in particular developing countries, including, by 2030, encouraging innovation and substantially increasing the number of research and development workers per 1 million people and public and private research and development spending.	

ANNEX 4: ANALYTICAL METHODS

Given the harmonised revision of the orphan and paediatric regulations together with the general pharmaceutical legislation along the same objectives, the methodology and models largely build on the impact assessment of the *general* pharmaceutical legislation[217].

1. Data sources

There have been multiple data sources and related analytical methods applied to provide evidence for the impact assessment of the orphan policy elements and options.

Literature and document review: we have carried out a targeted literature and document review of academic and grey literature, using specific topics of each policy option, such as access to medicines, to guide our searches. There is a growing body of published literature and analysis reports that studied specific phenomena relevant to aspects of the pharmaceutical legislation. These provide a direct source of facts and figures that we used in our assessments and referenced across the report. Wider literature relevant to newer challenges for the pharmaceutical industry were also reviewed in order to identify future proofing challenges, resilience of supply chains, new manufacturing methods, combination products, digitalisation, new evidence requirements by regulatory authorities and environmental protection.

Secondary data analysis: quantitative data collected along the medicinal product lifecycle was analysed to derive a set of indicators and feed quantitative modelling of various policy scenarios. For problem analysis and baseline, we used data, where available, for the period of 2005-2020 from the IQVIA MIDAS dataset, Informa Datamonitor and Pharmaprojects, EMA's central Marketing Authorisation Application dataset, MRI decentralized / mutual recognition procedures database and EudraGMP.

Key challenges: All methods applied to our research encountered a varying degree of difficulty in relation to lack of quantitative data available in the databases and sources examined. Despite a growing body of literature and evidence in several relevant areas, we did not find enough data to quantify all relevant impacts of every policy measure discussed in the policy options for the future of the legislation. Whenever possible, we have made reasonable assumptions to assess the impacts, but this lack of quantitative data is a key limitation to our analysis.

2. Identifying and selecting significant impact types

We carried out an initial screening of the 35 impact types set out in the Better Regulation toolbox to identify the impacts the study will be reviewing more in depth for each policy block with each policy option. We used findings from the various analytical strands and data sources to identify all potentially important impacts, considering both positive/negative, direct/indirect, intended/unintended as well as short-/long-term effects. Specifically, our screening was based on the principle of proportionate analysis and considered the following factors.

- The relevance of the impact within the intervention logic
- The absolute magnitude of the expected impacts
- The relative size of the impacts for specific stakeholders
- The importance of the impacts for the EC's horizontal objectives and policies

[217] Staff Working Document – Impact assessment on the general pharmaceutical legislation (Annex 4).

- Any sensitivities or diverging views

This screening identified 8 of the 35 impact types as being of most significance for this impact assessment and therefore a deeper assessment was appropriate for the following key impact types:

- Conduct of business
- Administrative costs on businesses
- Position of SMEs
- Sectoral competitiveness and trade
- Functioning of the internal market and competition
- Innovation and research
- Public authorities
- Public health & safety and health systems

3. Modelling changes in market exclusivity vis-à-vis regulatory data and market protection system

a. Protection types and length in a sample of medicines

A basket of 217 products was selected based on IQVIA Ark Patent Intelligence data where the loss of protection (LOP) date was between 2016-2024 in four countries: France, Germany, Italy, and Spain. We chose this sample because in earlier years the regulatory protection system was not fully harmonised due to the legacy of the pre-2005 system. This sample has an additional benefit of having a prospective feature, in that it shows, based on empirical data, the composition of the most recent and also the expected future protection expiries of medicinal products.

In the basket, there have been 26 orphan medicines, and Figure 1 demonstrates how the protection types and lengths vary among them. These tables omit regulatory data and market protection (RP) because in the case of an orphan medicine the 10-year RP protection is matched by the 10-year market exclusivity protection (ME). Despite the same nominal lengths, the ME allows a couple of months longer protection, because it does not allow (yet) generic medicines to apply for authorisation before ME expiry. RP permits generics to start the authorisation earlier, so they can enter the market right after protection expiry.

Figure 10 – Length of protection of orphan medicines by type of protection

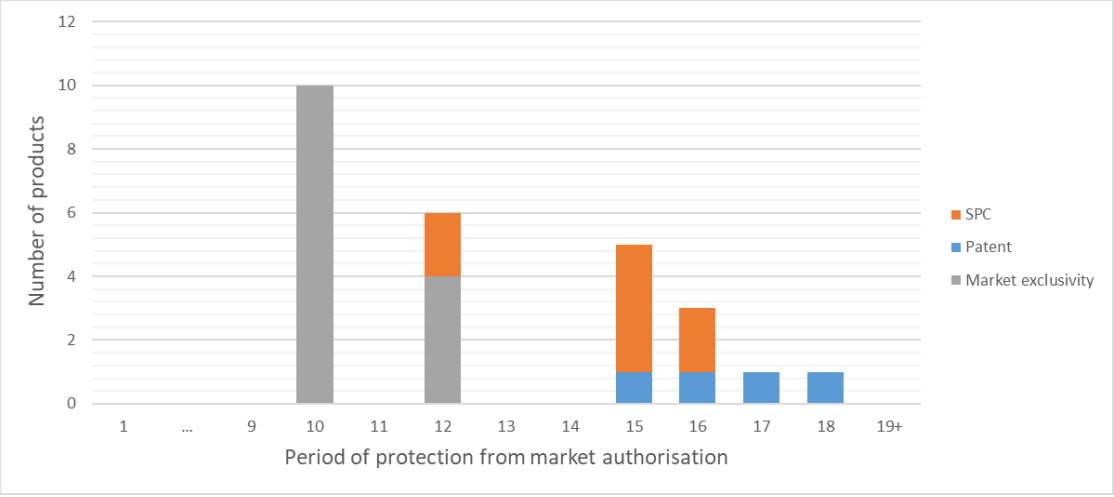


Table 24 - Length and type of protection of orphan medicines

	Years of protection after market authorisation											
Last line of protection	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19+**	**Grand Total**	**Avg peak annual sales**
Market Exclusivity	10		4								**14**	€ 41.4 m
SPC			2			4	2				**8**	€ 475.8 m
Patent						1	1	1	1		**4**	€ 248.0 m
Grand Total	10		6			5	3	1	1		**26**	€ 206.8 m

Similar to the findings of the general pharmaceutical impact assessment, Table 1 demonstrates that SPC and patent protected medicines have a longer protection type, and usually generate higher revenues, whereas products with ME are characterised by shorter protection (10 or 12 years if paediatric studies have been carried out) and lower revenues. In our sample, market exclusivity protected products (14 out of 26) make up more than 50% of all products, but only 11% of the total sales.

Consequently, changes to the market exclusivity (unless making it longer than SPC protections) would not affect SPC and patent protected medicines, thus limiting the economic impacts at systemic level. Nevertheless, changes may have significant impact on certain affected companies.

b. Developing an 'analogue' representing an innovative medicinal product lifecycle

In the general pharma impact assessment a key foundation of the model is a carefully crafted analogue. The analogue takes longitudinal sales data from a basket of medicines that meet certain criteria. For the general pharma this basket was made of RP protected medicines, however orphan medicines with 10-year protection were also eligible for inclusion. The analogue was generated from the weighted and normalised average sales values (in euros) and volumes (in standard therapeutic units) of the medicines in the cohort. To put it simply, the analogue behaves as a typical representative of that basket.

The analogue captures the lifecycle of innovative products over the protected period and that contested by generic/biosimilar medicines after protection expiry. Since ME protected medicines are similar to RP protected medicines in that they also have 10-year protection, and because they have been already included in the general pharma analogue, we have decided to use the same analogue with a slight adaptation. This adaptation is necessary due to the lower revenue generating capacity of non-SPC protected orphan medicines, a different avg. peak annual sales value is needed than in the RP model. After filtering out some very low sales (less than 10M) orphan medicines from the cohort, we have found an avg. peak annual sales of €80 m for ME protected medicines.

In order for sales revenues (euros) and volumes (standard units) across the pre-expiry and post-expiry cohorts and periods can be joined up and compared, aggregate absolute values were normalised so that the originator products' total sales and volume become equal to 100 at one year before protection expiry (Y-1).

A particular challenge is that sales revenues do not give the full picture of company benefits. The driver of businesses economic activity is not the revenue but the profit. Gross profit appears the most adequate and comparable measure, it is the cost of sales deducted from the revenues. The gross

profit only includes the variable costs of manufacturing and distribution, but not the fixed costs, such as R&D and investment in infrastructure. In our model we distinguish three categories of revenues, each with a different margin of gross profits.

- **Protected originator sales**: this is the most profitable category during the protected period of new medicines. Based on a sample of reports from publicly listed companies we apply a 80% gross profit margin on the revenues (20% cost of sales)

- **Contested originator sales**: once generics enter the market, originator products are forced into price competition. Still, originator products can maintain a price premium compared to generics albeit reduced thanks to brand loyalty and strong sales force. We assume a 50% gross profit margin in this category.

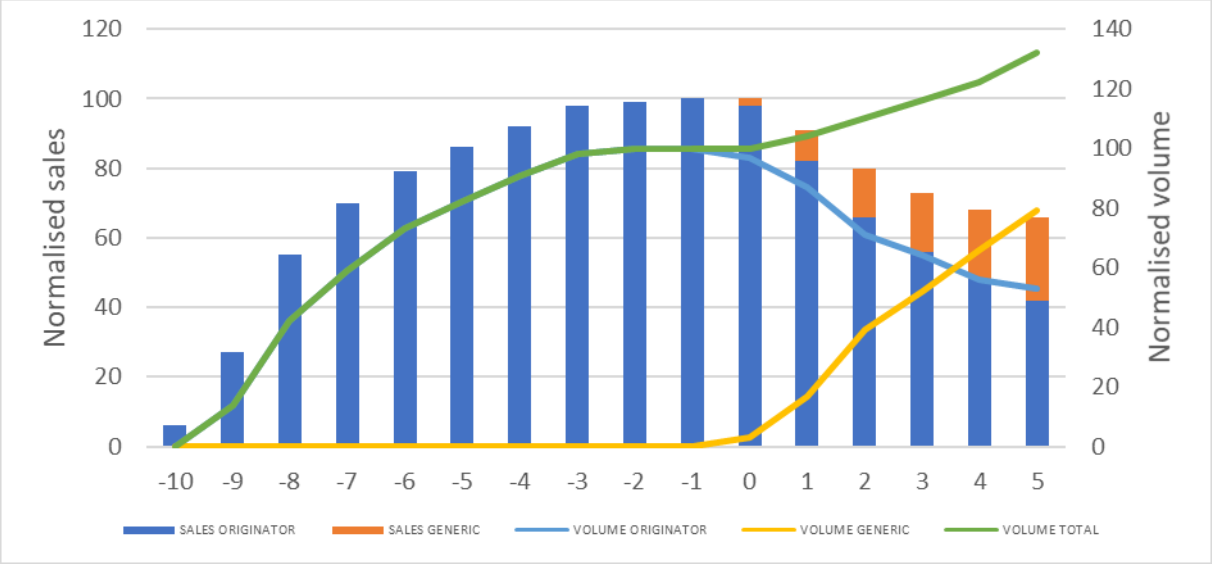
- **Generic sales**: generic industry operates on a high volume, low margin basis. With low product development risk, a lower profit margin can be sustainable. We apply a 33% gross profit margin on generic revenues.

The resulting table and corresponding figure are shown below:

Table 25 - Normalised sales, volume, gross profit and price for products with ME as last measure of protection

Year from expiry	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0	1	2	3	4	5
Originator sales	6	27	55	70	79	86	92	98	99	100	98	82	66	56	48	42
Generic sales											2	9	14	17	20	24
Total sales	**6**	**27**	**55**	**70**	**79**	**86**	**92**	**98**	**99**	**100**	**100**	**91**	**80**	**73**	**68**	**66**
Originator volume	0	14	42	59	73	82	91	98	100	100	97	87	71	64	56	53
Generic volume											3	17	39	52	66	79
Total volume	**0**	**14**	**42**	**59**	**73**	**82**	**91**	**98**	**100**	**100**	**100**	**104**	**110**	**116**	**122**	**132**
Originator profit	4.8	21.6	44	56	63.2	68.8	73.6	78.4	79.2	80	49	41	33	28	24	21
Generic profit											0.66	2.97	4.62	5.61	6.6	7.92
Originator price		1.93	1.31	1.19	1.08	1.05	1.01	1.00	0.99	1.00	1.00	0.94	0.93	0.88	0.86	0.79
Generic price											0.67	0.53	0.36	0.33	0.30	0.30
Average price		1.93	1.31	1.19	1.08	1.05	1.01	1.00	0.99	1.00	1.00	0.88	0.73	0.63	0.56	0.50

Figure 11 - Normalised sales and volume for products with 8+2 years of RP protection (baseline)



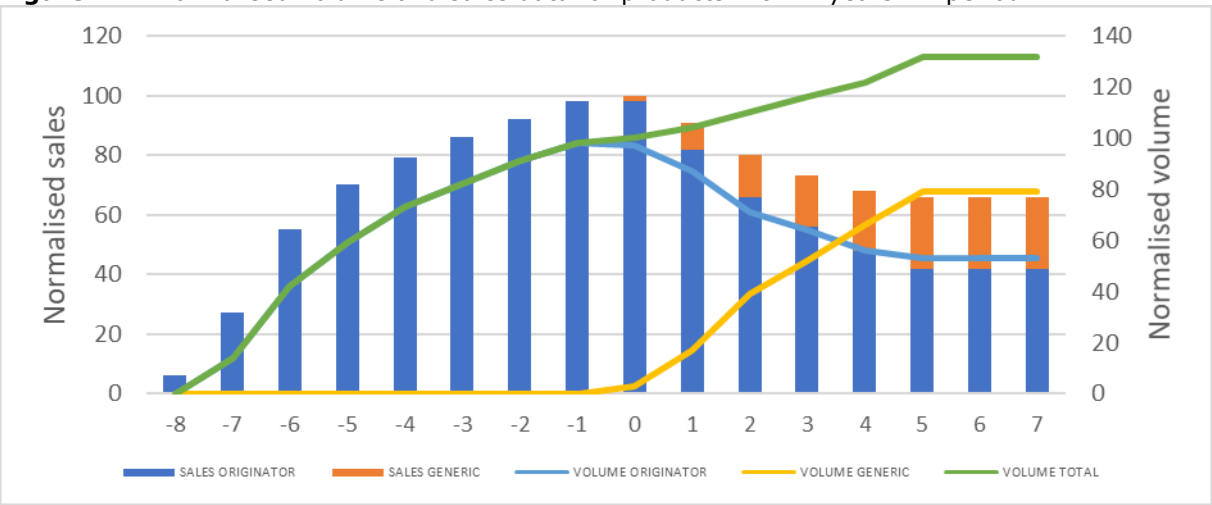
It is evident from the graph that sales revenue and volume grow year-on-year over the 10-year RP period as (i) the product is taken up by the health system and make it accessible to increasingly more patients; and (ii) product is launched in increasingly more member states. It should be noted that health systems may require a number of years before the product becomes accepted by health professionals and routinely prescribed. However, these effects are expected to reach a plateau within a couple of years of introducing the product in a market, and indeed the figure shows that by Y-3 sales figures are close to peaking. The last year before expiry therefore accounts for 14% of total protected sales; while the final two years account for 28% of total protected sales.

c. Modelling the economic impact of decreasing regulatory protection

Some options and common elements include a reduction of the length of market exclusivity. Because even in the revised general pharma regulation the RP would ensure a minimum 8-year protection for all medicines, the maximum lost protection due to shortened market exclusivity is 2 years. This will be the new scenario for the analogue. In the model, we assume that after 5 full years of generic competition an equilibrium value of annual sales and volume of product sold are established and thus we can use Y5 data for originator and generic products as long-term level to calculate the value of ME loss over the product lifetime.

We also assume that the pre-expiry sales trajectory is not changed by company behaviour and thus the baseline Y-1 and Y-2 sales are lost under the new standard ME regime. In the figure below thus the original Y-1 and Y-2 values are removed and Y6 and Y7 values are added at equilibrium level. In addition, we assume that the market dynamics of generic competition (between Y0 and Y5) in the new standard ME regime will not change compared with the ME period of 10 years.

Figure 12 - Normalised volume and sales data for products with -2 years ME period



	Baseline	-2 years ME	change	change %
Originator protected sales	712	513	-199	-28%
Originator contested sales	392	476	84	21%
Originator profit	765.6	648.4	-117	-15%
Generic sales	86	134	48	56%
Generic profit	28.38	44.22	16	56%
Cost to public payer	1190	1123	-67	-6%
Volume (patients served)	1343	1407	64	5%
Cost of additional patients	0	44	44	
Cost of baseline volume	1190	1079	-111	-9%

Using the above model for the product lifetime, we can make the following observations at product level:

- Originator companies' pre-expiry sales loss of -199 (normalised units) over two years is partially compensated by the post-expiry gain of +84 (calculated at the equilibrium level) over two years, giving a net loss of -115 (normalised units) over the lifetime. In other words, originators lose 28 % of their protected sales when the protection is shortened by 2 years. This translates to a decrease in originator's gross profit of -117 (normalised units), which is a 15% loss over the product lifetime, approximated as a 16-year period.

  We know that pharmaceutical industry is one of the most R&D intensive sector and they reinvest a large share of their revenue into innovation for new products and technologies. This share is 20% on average globally[218] and we can assume that the revenue loss will translate to a loss of innovation budget and thus a loss of development of new innovative products and/or incremental (i.e. cheaper) product innovation (e.g. for combination products or new formulations).

[218] See https://www.drugdiscoverytrends.com/pharmas-top-20-rd-spenders-in-2021/

- Generic companies' start to benefit from sales two years earlier compared to baseline, and thus reach equilibrium level two years earlier. These two extra years of equilibrium generic sales of +48 (normalised units) are equal to +16 (normalised units) gross profit gains.
- Healthcare payers pay less overall due to a decrease in the average price they need to pay for a standard unit of the product. In the baseline 10-year ME regime, the total lifetime sales is 1190 (normalised units) and in the new 8-year protection regime the same volume at the new prices would be 1079 (normalised units). Thus in the new situation healthcare payers would pay -111 (normalised units) less, which is -9% less when considering the lifetime sales of the product.

  In the real situation, however, healthcare payers may not realise this nominal saving but choose to purchase more units of the medicine at a lower price for the healthcare system and expand coverage of patients. This can be considered that payers 'reinvest' part of the savings in the same market and increase purchase of generic products at higher volumes for the benefit of the patient. We can thus calculate the total real sales of originator plus generics product volumes, which can be used to monetise patient benefit. Under the baseline situation, total sales value over the product lifetime is 1190 (normalised units), while under the 8-year protection regime it is 1123 (normalised units), equating to -67 (normalised units) or -6% saving to healthcare payers, on the products that are ME protected. Note, however, when considering the ME protected medicines represent less than 5% of the pharmaceutical expenditure, and that from the total healthcare systems spending in the EU, the pharmaceutical expenditure represents less than 20% (see Analytical report Figure AFF-3, OECD Health Statistics), the savings at the healthcare system level would be marginal.

- Patients benefit due to the increased volume of the medicine sold after ME expiry (2 years earlier) which then reach more patients creating higher level of health benefits. In the model, the total volume increases as soon as generic products enter the market and volume of generic products surpasses that of the originator product by year 4 after generic entry. In the new regime the total volume sold increases by +64 (normalised units) or 5% over the product lifetime above the baseline of 1343 (normalised units) under the 10-year ME regime. However, the extra volume of products available to patients manifest itself in the transition period between expiry and reaching the equilibrium value.

i. Monetising the systemic effects for protection loss due to abolishing ME (Option B)

Option B would result in a 1-year protection loss for orphan medicines that are launched in all EU countries and a 2-year loss for those that are not, because of the revised regulatory protection in general pharma. In accordance with baseline projections, we expect 10 orphan medicines annually where the market exclusivity is the last layer of protection of these, we expect that 4 would comply with market launch in all Member States and 6 would not. Table 7 shows the economic impacts per stakeholder.

Table 26 – Economic impact of no market exclusivity in combination with changes of regulatory protection

	Product level change 1 year loss	Product level change 2 years loss	Systemic change (4 all-EU launch, 6 not all-EU)
Originator gross profit	**-€47m**	**-€94m**	**-€751m**
Generic gross profit	**+€6m**	**+€13m**	**+€101m**
Cost to public payer	-€27m	-€54m	-€430m
Δ of patients treated (monetised)	+€21m	+€35m	+€295m

Patients + payer monetised gain/loss	**+€48m**	**+€89m**	**+€725m**

Note: colour code shows increased benefit/reduced cost (green) or decreased benefit/increased cost (red) to the stakeholder

Option B would generate an annual €430m savings to public payers, and with the additional patients served thanks to earlier price competition, the public saving amounts to €725m a year (over the annual €40-50bn that the EU spends on orphan medicines). Apart from supporting affordability, this option also contributes to improving access by allowing the incentive introduced in the general pharmaceutical legislation to affect orphan medicines.

For developers of orphan medicines, the direct impact of abolishing the incentive would be €751m in lost profits. This impact would be amplified by the message transmitted to patients, researchers, companies and investors active in the rare disease area. Divestments and shifting research priorities would likely withdraw resources from orphan medicines development and would be negatively perceived by all stakeholders.

ii. Monetising the systemic effects for protection loss due to not launching in all EU markets (Option C)

Option C offers the same market exclusivity period for standard orphan medicines as the baseline, 10 years, but only if the medicine is launched in all EU markets within 2 years of authorisation. If not launched in all markets, the protection period is 9 years. This aims to motivate companies to launch in all EU member states, and not to leave out small markets, which are not attractive enough commercially. Similarly to the general pharma revision, it is expected that some medicines will not comply with the access incentive conditions. Given the lower level of baseline compliance of orphan medicines reliant on ME compared to non-orphan medicines reliant on RP, the gap to be bridged will be larger. The assumption is therefore made that 40% of orphan medicines will comply (for non-orphans it is 50%[219]), and 60% will not. Thus, of the 10 orphan medicines expected to have ME as last line of protection, we expect that 4 would comply with market launch in all Member States (and 6 not).

If a standard orphan medicine is **launched in all EU member-states**, the reward will have the same economic impact as in the baseline, with the 10-year market exclusivity protection.

No distinction is made here between HUMN and non-HUMN ME-reliant orphan medicines (the total of 10 includes both), since in either case, the length of protection will be increased by one year if the access conditionality is met as compared with those that do not comply. The table below therefore accounts for both cases. Using our model, the impact of 1-year less protection in case of non-launch in all Member States is the following:

Table 27 – Impact of change of -1 year market exclusivity in case of non-launch in all MS

	Product level change	% change	Systemic change (6 medicines)
Originator gross profit	**-€47m**	**-7.7%**	**-€282m**
Generic gross profit	+€6m	+28%	+€38m
Cost to public payer	**-€27m**	**+2.9%**	**-€162m**
Δ of patients treated (monetised)	+€21m	+2.4%	+€126m
Patients + payer monetised gain/loss	+€48m	+5.0%	**+€288m**

[219] General pharma IA SWD, Section 8.1.

For the public payer/patient this instrument is a win-win, if medicines comply, timely access across the EU will increase, and if not, the protection period decreases, lowering cost for society by 48m. The decreased protection translates to 47m lower gross profit per medicine, or 282m for the whole innovative industry.

iii. Monetising the systemic effects for protection loss due to allowing day-1 generic entry (common element)

Allowing entry of generic medicines as soon as market exclusivity is expired, means that an **application for authorisation** of a generic version of the medicine **can be submitted** during the protection period, and can enter the market right after expiry of the market exclusivity. Currently, generic versions of orphan medicines cannot start the authorisation process before the market exclusivity expires[220]. This creates a windfall protection of at least 9 months beyond the 10 years ME, equal to the time needed to authorise a generic medicine from submission[221]. It is estimated that 10 out of the expected 25 new orphan medicines would be impacted per year, the ones where ME is the last layer of protection. Apart from legal certainty for generics it would mean up to €360m savings to the public. Originators would lose their windfall profits by €354m. See Table 11 for the financial impacts of day-1 entry of generic medicines on all stakeholders.

Table 28 – financial impacts of day-1 entry of generic medicines	**Systemic change (10 medicines)**
Originator gross profit	**-€354m**
Generic gross profit	+€50m
Cost to public payer	**-€200m**
Δ of patients treated (monetised)	+€160m
Patients + payer monetised gain/loss	**+€360m**

iv. Monetising the systemic effects for protection loss due to abolishing paediatric ME extension (common element)

Abolishing the orphan market exclusivity extension[222] for completing PIPs will better regulate a system that is currently not functioning very well. At present, the paediatric regulation offers 6 months of SPC extension for completing a PIP, and for orphan medicines 2 years of market exclusivity extension. However, there are several SPC protected orphan medicines with 13-14-15 years of protection duration[223]. Obviously, for these products a 10+2 years market exclusivity is of less value and they would be better off with a 6 months extension of the SPC protection. To switch to this protection, they need to renounce their orphan designation and they often do so. The abolition of the paediatric extension of market exclusivity is thus expected to improve clarity in the system.

Table 29 – Impact of abolishing 2 years ME extension for completed PIP	**Systemic change (1 medicine)**
Originator gross profit	**-€94m**
Generic gross profit	+€13m

[220] See also Section 5.2. of this SWD (common elements).
[221] This is different to the general pharma legislation, where regulatory data protection is designed in a way to allow generic filing before expiry.
[222] This measure is regulated in the Paediatric Regulation and it is mentioned as a common elements of the revision of the paediatric legislation, however it changes the market exclusivity period, therefore its impact is relevant for orphan products therefore it is discussed in this section.
[223] See also Table 3 (length of protection of orphan medicines by type of protection).

Cost to public payer	**-€54m**
Δ of patients treated (monetised)	**+€42m**
Patients + payer monetised gain/loss	**+€96m**

The measure will also imply that orphan medicines not protected by SPC but eligible to complete a PIP, will lose the 2-year extra market exclusivity protection available in the baseline. However, from the entry into force of the Paediatric Regulation up to 2020, only 11 of these market exclusivity extensions were granted[224], meaning that it has been a rarely used incentive. With 1 such incentive not granted per year in the future, the public would save €96m per year. The affected originator companies would lose €94m in gross profits over the medicine's lifetime each, but due to the few uses, the impact on the whole industry is not significant.

Caveats to the model used:

Data: IQVIA MIDAS data includes sales revenue data corresponding to list or ex-manufacturer price without accounting for rebates or discounts (especially in hospital sector) on the one hand and costs including wholesale, distribution, value-added tax and social security expenses on the other to healthcare payers.

Opportunity cost: We present data at current euro level without inflation or cost of capital / commercial risk accounted for. This latter is a factor for commercial actors where monetary gains and losses are normally discounted in business calculations and may change decisions related to product developments accordingly. In contrast, healthcare payers pay on an ongoing basis.

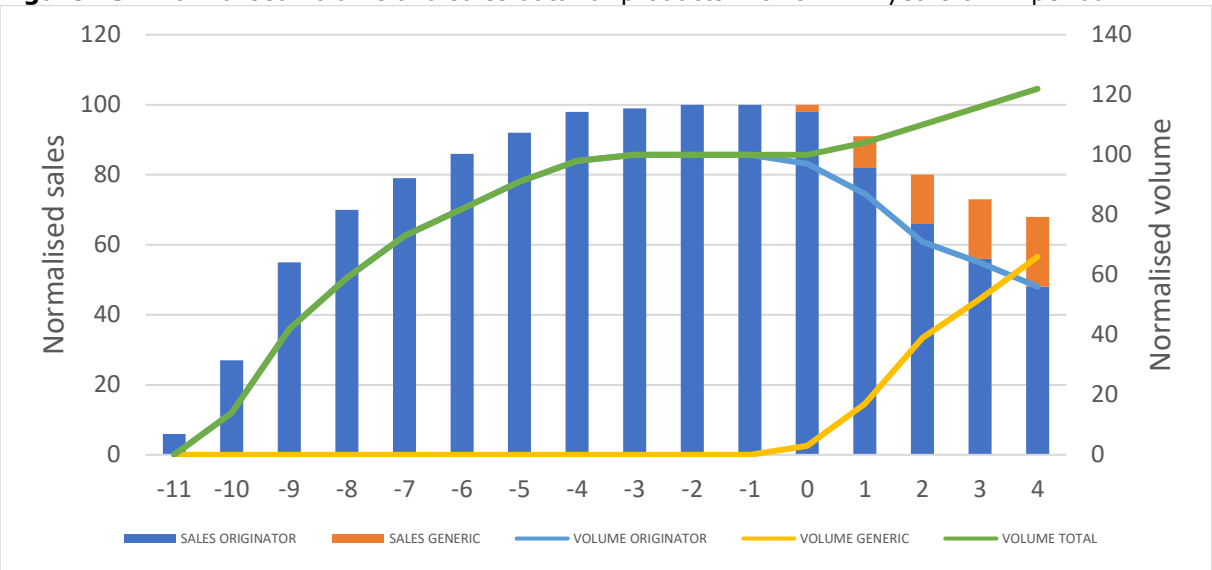
Business behaviour: There may be changes in the trajectory pre- or post-expiry compared to the current RP 8+2 regime, because companies change behaviour and aim to earn similar level of total pre-expiry monopoly rent during the reduced RP period. This may be achieved by entering more markets earlier leading to the same pre-expiry overall sales and volumes of product sold. There is however the risk that the shorter RP period will lead to higher negotiated prices and relatively lower volumes of product sold in the pre-expiry period, or even a reduction in the number of products that enter EU markets.

d. Modelling the economic impact of increasing market exclusivity protection

We use the same data as presented above and assume that after the Y-1 there will be an additional year of peak sales protected by a 1-year ME period. We will use the result of this model to estimate the proportionate effect of the 1 year incentive for HUMN addressing medicines. We assume that pre-expiry sales trajectory is unchanged, the market dynamics of generic competition post expiry is unchanged. In the figure below thus data associated with a new Y-1 is added and the baseline Y5 is removed to maintain the overall product lifetime of 16 years.

[224] EMA data.

Figure 13 - Normalised volume and sales data for products with 8+2+1 years of RP period



	Baseline	+1 year ME	change	change %
Originator non-contested sales	712	812	**100**	14.0%
Originator contested sales	392	350	**-42**	-10.7%
Originator gross profit	765.6	824.6	**59**	7.7%
Generic sales	86	62	**-24**	-28%
Generic gross profit	28.38	20.46	**-7.9**	-28%
Cost to public payer	1190	1224	**34**	2.9%
Volume (treated patients)	1343	1311	**-32**	-2.4%
Patients + payer monetised gain/loss	1190	1241	**51**	4.3%

Note: colour code shows increased benefit/reduced cost (green) or decreased benefit/increased cost (red) to the stakeholder

Using the above model for the product lifetime, we can make the following observations at product level:

- Originator companies increase pre-expiry sales due to additional year of monopoly sales by 100 (normalised units) or 14% of lifetime protected sales. In terms of gross profit, this is 47 more monetised unit, or a 7.7% increase.
- Generic companies' start to benefit from sales one year later, and thus generic sales are reduced by 24 (normalised units), and gross profit is reduced by 8 (normalised unit) which is equal to a reduction of 28% sales, compared to baseline.
- Healthcare payers pay more overall due to an increase in the average price they need to pay for a standard unit of the product. We consider again the 'peak' volume sold of the originator product pre-expiry in baseline and use the average price in each year under the different RP regimes to calculate sales. The total cost for healthcare payers is thus -51 (normalised units) over the product lifetime compared to baseline
- Patients lose -32 (normalised units) in decreased volumes of the medicine over the lifetime of the product compared to baseline

i. Monetising the systemic effects for 1-year ME extension for medicines addressing HUMN (Option C)

In accordance with baseline projections, we expect that from the 10 orphan medicines annually where the market exclusivity is the last layer of protection, this measure would affect 20% or two products, which would address HUMN and therefore be eligible for the extra year.

Table 30 – Impact of change of +1 year market exclusivity protection

	Product level change	% change	Systemic change (2 medicines)
Originator gross profit	**+€47m**	**+7.7%**	**+€94m**
Generic gross profit	-€6.5m	-28%	-€13m
Cost to public payer	**+€27m**	**-2.9%**	**+€54m**
Δ of patients treated (monetised)	**-€14m**	-2.4%	**-€28m**
Patients + payer monetised gain/loss	**-€41m**	**-4.3%**	**-€82m**

Note: colour code shows increased benefit/reduced cost (green) or decreased benefit/increased cost (red) to the stakeholder

We estimate that an average orphan medicine addressing HUMN and relying on market exclusivity as last line of protection will be able to generate €47m more profit (or 7.7% more than in baseline). Such medicines will become more attractive commercially for developers, and their proportion among the newly authorised medicines would increase. We estimate that instead of the 75 projected HUMN addressing orphan medicines in the dynamic baseline (Section 5.1), there would be 80-85 HUMN products authorised in the next 15 years.

The cost of a +1 year protection for HUMN protection would be shared among generic industry, health payers and patients. With 2 of such incentives annually, the generic industry would lose €38m in revenues a year, which translates into €13m decrease in gross profits. The health payers would need to pay €54m more on an annual basis. The model also accounts for the patients that would not be served due to the higher prices that result from extended protection. Accounting for that effect too, the cost for the public would rise by €82m annually.

Apart from the monetary impacts stemming from the increased market exclusivity period, we also estimated the number of additional medicines coming to the market. The incentive has two effect: (1) it generates more resources for innovators, (2) it makes the EU market more attractive to medicines that otherwise would not come to the market (there are several orphan medicines annually that are only launched in the US market and not in the EU). As a result of subtle and complex effect pathways, we could not identify directly available literature evidence or model. F

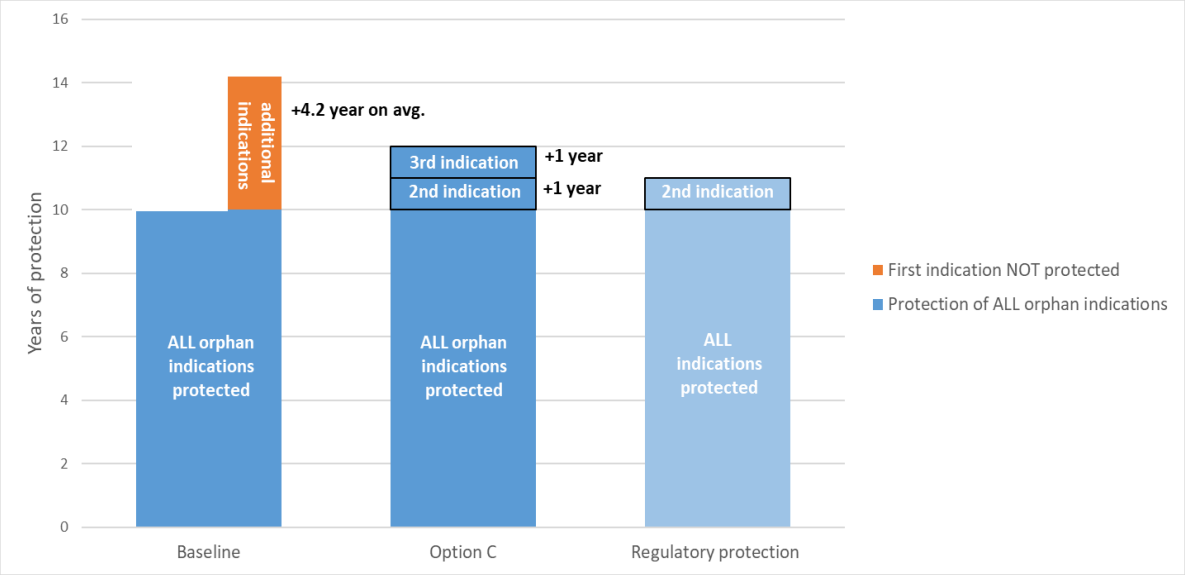
4. Global marketing authorisation

The introduction of the global marketing exclusivity (GMA) will limit stacking market exclusivity periods for additional orphan indications. GMA prolongs the existing market exclusivity by only 1 year in all orphan indications. The use of this incentive is maximised at two indications, i.e. maximum 2 years of prolongation of the ME will be possible. Furthermore, market exclusivity granted **to a second generation product** that is similar to the first generation product will not be applied in respect of generic products of the first reference product for which the market exclusivity expired to avoid so called evergreening[225].

[225] See also Section 5.2 of this SWD.

The GMA would concern 16% of orphan medicines, those with multiple orphan indications. For them it would mean replacing 4.2 years of partial protection for additional indication with on average by 1.3[226] years complete protection of the medicine. Importantly, this would put a limit on 'orphan blockbusters' with several indications, and disincentives on gaming the system for artificially inflated protection periods.

Figure 14 – protected indications under GMA and RP



5. Regulatory data protection vouchers

Overview

Option A envisages a transferrable regulatory voucher as an incentive for originators of products that address high unmet need (HUMN) in rare diseases and diseases in children. The voucher would grant a one-year RDP extension for one medicine. The company awarded the voucher would be allowed to sell on the voucher to another company. For the voucher to be of value, the purchaser must hold a medicine that is reliant on RDP as last line of protection. For products where the SPC or patent expires a year or more after RDP, such a voucher would be of no value.

This section sets out the methodology used to calculate the impact of a voucher scheme for various stakeholders. The analysis highlights the key shortcoming of this form of incentive, namely that the rent generated by the voucher will be shared between the voucher seller and the voucher buyer. Moreover, as the number of vouchers issued increases, the share of the seller declines very quickly. However, the reward to the seller is the intention of the scheme. The reward to the buyer is a by-product. Vouchers come at a significant cost to public authorities, who have to a protection premium on the medicines that use them for an additional year. The more of that additional expenditure that goes to the buyer rather than the seller, the less efficient the scheme.

[226] The weighted average of protection for medicines with one or more additional indication

The methodology set out below aims to simulate the economics of a market for vouchers on the basis of real world data and thereby estimate the shares of voucher rent that would accrue to buyers and sellers respectively. It results in the conclusion that the scheme would become highly inefficient given the number of vouchers that would have to be issued for HUMN products for rare diseases alone (3-6 per year) and all the more so if they were also issued to reward UMN products for children (5-6 per year). As well as being inefficient, such a scheme, by overloading the market with vouchers, would undermine the efficiency of any future scheme to award vouchers for novel antimicrobials. This class of products would be better adapted to this form of reward as it would entail issuing one – or at most – two vouchers per year.

As well as being costly to public authorities, RDP extension vouchers, by delaying the decrease in the price of those medicines, delay the increase in their uptake, which comes at a price to patients. This effect is measured along with the additional cost to public authorities in the calculations set out below.

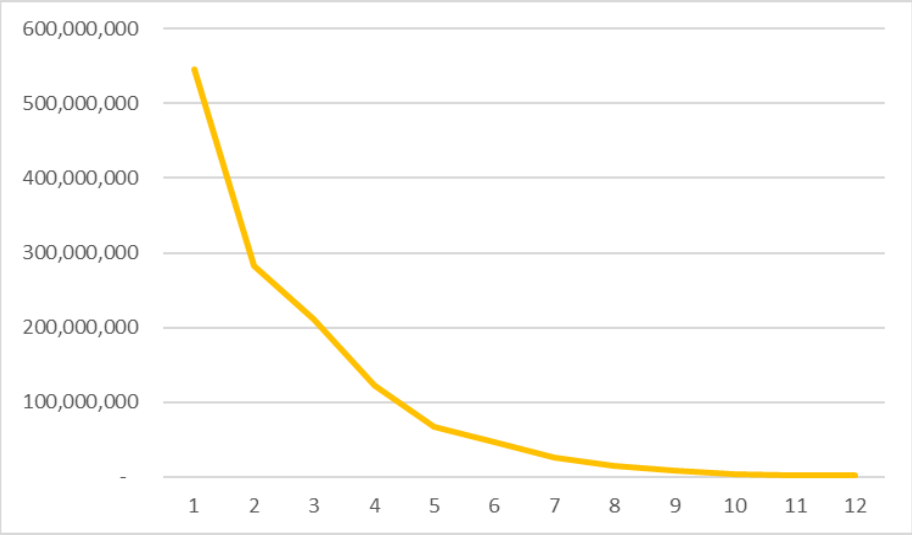
Methodology

The cost to payers and the share of those additional costs that accrues to voucher sellers (i.e. to HUMN originators) is calculated in the following way. First, a representative annual cohort of RDP-protected products is constructed based on IQVIA sales data. This will give the profile of the potential voucher buyers. From this can be inferred the cost of a given annual number of vouchers to public authorities, the share of this expenditure that will go to the intended recipient i.e. the voucher seller, and the cost to patients in the form of lower uptake.

The RDP-protected products with expiry over an 11-year period (2014-2024) were used to construct the representative cohort. First, the medicines are each assigned to their respective annual cohorts. Second, the medicines with expiry in the same year were ranked according to the value of EU sales in the top selling year for each medicine according to IQVIA data. The average peak sales value of the top product from each year group gives the peak year sales value of the top product in the representative sample. The average value of the second product from each year group gives the peak year sales value of the second product in the representative sample and so on.

Table 31 – Peak sales of products in the representative annual cohort

Product	Peak sales
1	545 000 000
2	282 654 545
3	210 890 909
4	122 727 273
5	66 854 997
6	46 362 340
7	25 833 879
8	14 449 938
9	9 270 111
10	3 555 616
11	2 021 996
12	1 807 804



A model based on the decline in revenue experienced by a representative RDP-protected product after protection expiry is used to calculate the cost and benefit to various stakeholders of a one-year exclusivity extension for such a product. Table 32 illustrates the calculation of the value of a

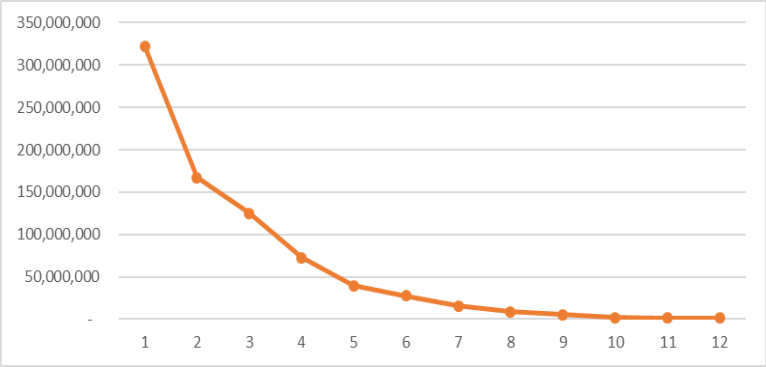
voucher to a voucher buyer, taking as an example the top selling product in the representative cohort.

Table 32 – impact of a voucher on stakeholders, expressed as a percentage of peak year sales of the medicine for which the voucher is bought

	Baseline	Voucher	Change	Change %
Originator sales	981	1063	82	8%
Generic sales	130	100	-30	-23%
Cost to public payer	1111	1163	52	4.7%
Cost of baseline volume	1111	1192	81	7.3%
Patients served	1445	1390	-55	-3.8%
Originator volume	1059	1111	52	
Originator distribution cost	212	222	10	
Net marginal revenue (NMR)	769	841	72	9%
Net present value of NMR			59	

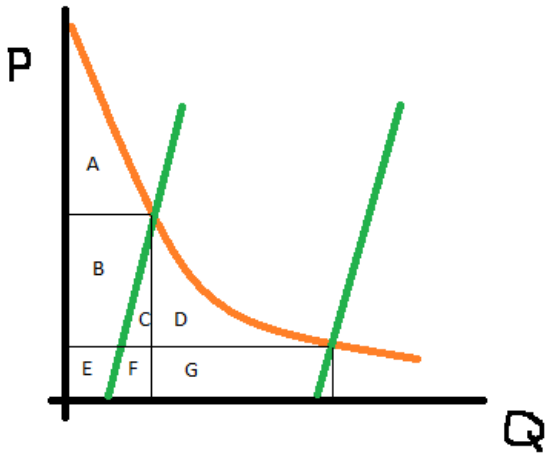
The change in net marginal revenue of the originator (i.e. the voucher buyer) gives the value of the voucher for each buyer and therefore the willingness to pay of each potential buyer. It is thus possible to construct a demand curve for the market for RDP extension vouchers.

Figure 15 – demand function for vouchers



Given this demand function, the supply curve (whose position depends on the HUMN criteria) will determine the equilibrium price.

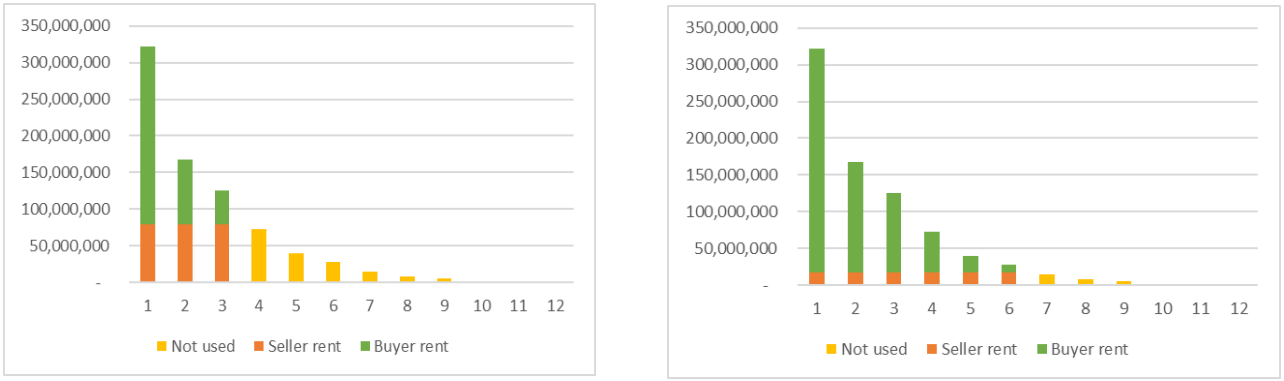
Figure 16 - equilibrium price for vouchers



The supply function can be represented as a vertical line or, arguably, as a steep upward sloping line reflecting the incentive impact of the scheme. Given the shape of the demand curve, the price drops sharply as the number of vouchers increases from one to three to five. In Figure 16 the rent represented by areas B and C go to the voucher seller with a smaller number of vouchers. With a larger number, B and C go to the buyer, along with D. The seller is left with only E, F and G.

In Figure 17 the analysis applied to the representative cohort. Thus, with one voucher issued, the seller's share of the voucher rent is 57%. With three, it is already less than the buyer's share at 39%. With six, it is only 13%, with the remaining 87% wasted on benefits accruing to companies that are not the intended beneficiaries of the scheme.

Figure 17 – The seller and buyer share of voucher rent varies with the number of vouchers



While the originator's revenue increases with a corresponding increase in the expenditure by payers, this is in part offset by a decrease in the revenues of generic manufacturers. However, the implied cost is also an understatement, given that fewer patients will be served over the period considered as a result of higher prices. The cost of the catering to the higher number of patients served in the baseline at the prices seen in the policy scenario is higher.

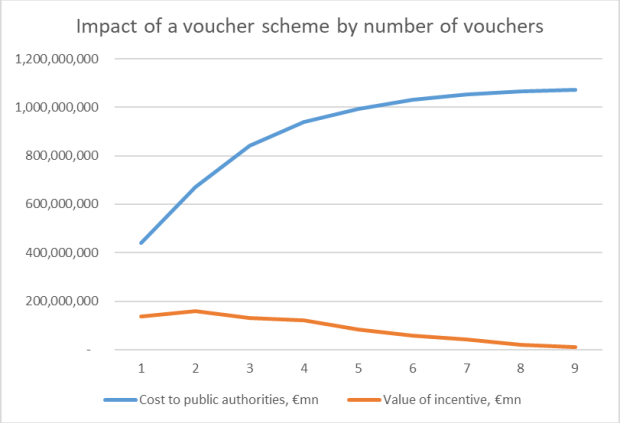
As explained above, there may be up to 6 HUMN medicines for rare diseases per year which would imply the use of six possible vouchers. The matrix below then gives a total annual combined cost to the public payer of **over a billion euros**.

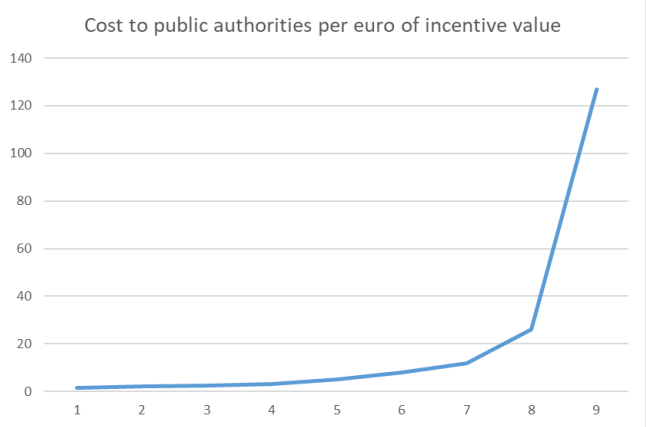
Table 33 – Number of vouchers and financial impact on health systems

# of vouchers	Peak sales	Cost of nth voucher to payers (81% of peak sales)	Cumulative cost to payers
1	545,000,000	441,450,000	441,450,000

2	282,654,545	228,950,182	670,400,182
3	210,890,909	170,821,636	841,221,818
4	122,727,273	99,409,091	940,630,909
5	66,854,997	54,152,548	994,783,457
6	46,362,340	37,553,495	1,032,336,952
7	25,833,879	20,925,442	1,053,262,394
8	14,449,938	11,704,450	1,064,966,844
9	9,270,111	7,508,790	1,072,475,634
10	3,555,616	2,880,049	1,075,355,682
11	2,021,996	1,637,817	1,076,993,499
12	1,807,804	1,464,321	1,078,457,821

Figure 18 – Cost to public authorities per euro of incentive value





A similar analysis has been set out in a paper that appeared in *Health Review* in 2016[227]. Some corroboration of this analysis can be seen from the US experience of issuing priority review vouchers for various classes of products. While a priority review voucher is a distinct mechanism, the effect of the number of vouchers would be similar, as more vouchers would mean that they would be used for less and less revenue-generating products. After what may have been a "teething phase" of the first two, the relationship between the number of vouchers and the price at which they are sold would appear to correspond to the above supply and demand based analysis.

Figure 19 - Number of PRV awarded by FDA

[227] The Commercial Market For Priority Review Vouchers | Health Affairs

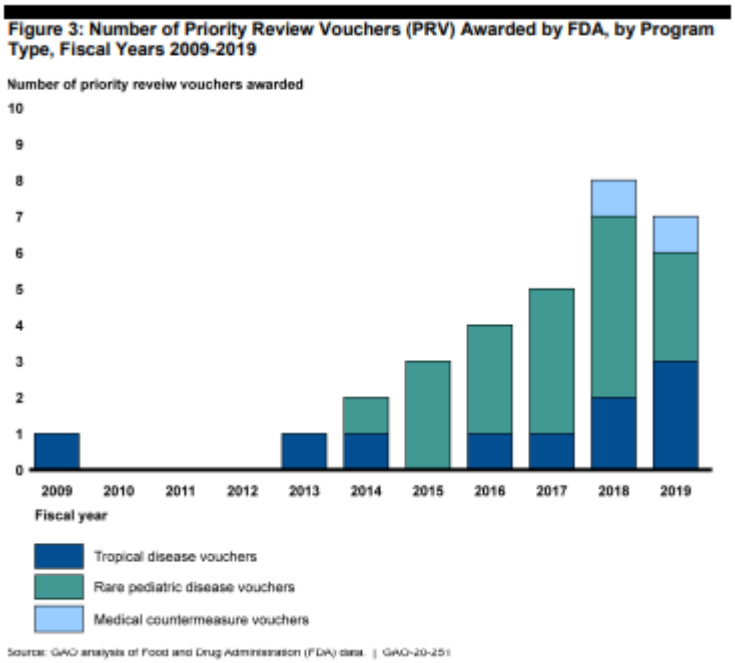
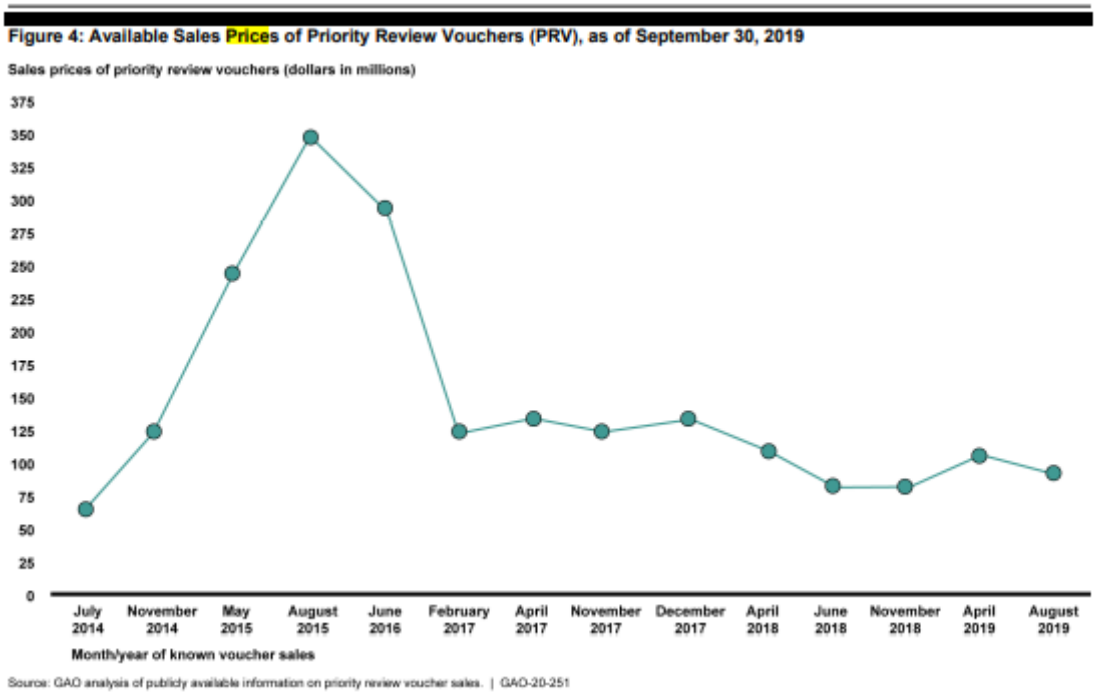


Figure 20: sales price PRV



6. *The impact of measures to improve market access*

The baseline takes account of the preferred option in the revision of the general pharmaceutical legislation, which makes the last year of RDP conditional on authorization in all Member States within two years. However, since orphan medicine originators will benefit from ten years of market exclusivity in the baseline, they will continue to enjoy ten years of protection from generic competition, even if they do not meet the condition. For this reason, Option C for the orphan

revision provides for a conditionality that matches the one that applies to RDP, so that the incentive extends to orphan products that rely on market exclusivity as their last line of protection. Option B, by eliminating market exclusivity has the same effect of allowing the incentive to apply to ME-reliant orphan medicines.

Table 34 - Regulatory protection and market exclusivity periods in different scenarios under Option A

Option A	**Not launched in all EU**		**Launched in all EU**		**Access premium**
	Regulatory protection	Market exclusivity	Regulatory protection	Market exclusivity	
Standard orphan medicines	8 years	**10 years**	9 years	**10 years**	0 year
HUMN orphan medicines	8 years	**10 years**	9 years	**10 years**	0 year

Table 35 - Regulatory protection and market exclusivity periods in different scenarios under Option B

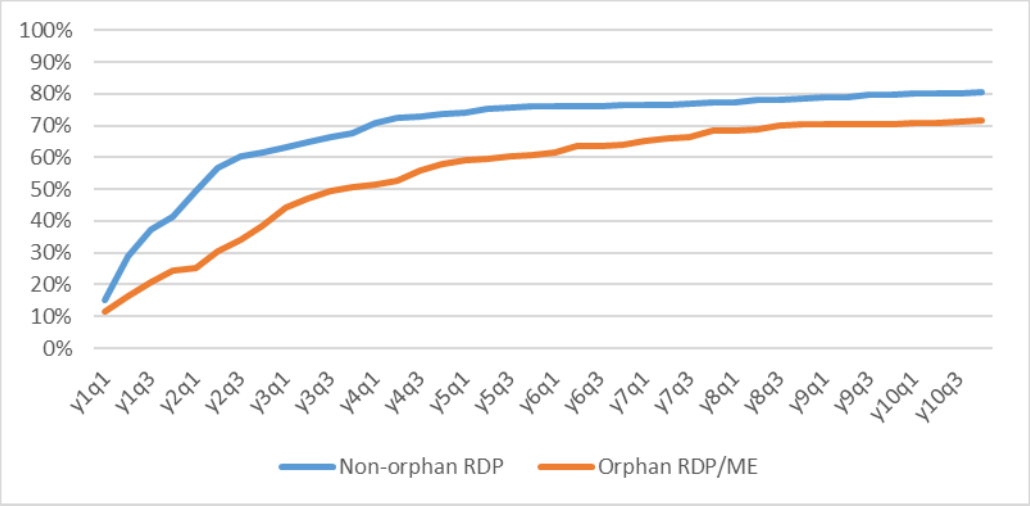
Option B	**Not launched in all EU**		**Launched in all EU**		**Access premium**
	Regulatory protection	Market exclusivity	Regulatory protection	Market exclusivity	
Standard orphan medicines	8 years	**0 years**	9 years	**0 years**	+1 year
HUMN orphan medicines	8 years	**0 years**	9 years	**0 years**	+1 year

Table 36 - Regulatory protection and market exclusivity periods in different scenarios under Option C

Option C	**Not launched in all EU**		**Launched in all EU**		**Access premium**
	Regulatory protection	Market exclusivity	Regulatory protection	Market exclusivity	
Standard orphan medicines	8 years	**8 years**	9 years	**9 years**	+1 year
HUMN orphan medicines	8 years	**10 years**	9 years	**11 years**	+1 year

IQVIA sales data was used to assess the baseline level of access to orphan medicines across 25 Member States[228] for orphan products in the relevant category (reliant on ME rather than SPC). For each molecule and each Member State, the first quarter in which meaningful[229] non-zero sales occurred for at least two successive quarters was taken to indicate the quarter in which the product reached that market. It was then possible to calculate for each products, how many Member States and what percentage of the EU population it had reached after a given number of quarters. Then, taking the average across all the products in the basket, we were able to plot the evolution of the average ME-dependent orphan product and compare it with that of the average RDP-dependent non-orphan product. To follow the evolution of market access over 10 years, the sample was restricted to only those products that are authorised between Q1 2010 and Q4 2011[230].

Figure 21 – Percentage of the EU population having access to the product overtime by protection type



The average ME-reliant orphan can be seen to fare considerably worse than the average RDP-reliant non-orphan. Not only is the final level of access lower, it is achieved more slowly. Deeper analysis point to higher coverage of products with higher sales and that larger member states with higher GDP tend to have a higher share of the products on their market.

Figure 22 – Percentage of population served over time

[228] NB. IQVIA MIDAS sales data were not available for Cyprus and Malta.

[229] At least 1% of the average EU per capita sales volume.

[230] The RDP-reliant non-orphan products in the basket were ABIRATERONE ACETATE, ACETYLSALICYLIC ACID!CLOPIDOGREL, AMLODIPINE!HYDROCHLOROTHIAZIDE!OLMESARTAN MEDOXOMIL, AMLODIPINE!TELMISARTAN, ASENAPINE, BROMFENAC, C1 INHIBITOR (HUMAN), CABAZITAXEL, CLEVIDIPINE, CORIFOLLITROPIN ALFA, DEXAMETHASONE, DEXMEDETOMIDINE, DUTASTERIDE!TAMSULOSIN, GIMERACIL!OTERACIL!TEGAFUR, METFORMIN!SAXAGLIPTIN, PITAVASTATIN, ROFLUMILAST, SILODOSIN, TAPENTADOL, THIOTEPA, VELAGLUCERASE ALFA
The ME-reliant orphan products were ANAGRELIDE, CLOFARABINE, DECITABINE, DEFIBROTIDE, ICATIBANT, MECASERMIN, MIFAMURTIDE, NELARABINE, STIRIPENTOL, TEDUGLUTIDE, THIOTEPA, VELAGLUCERASE ALFA, KETOCONAZOLE, MERCAPTOPURINE

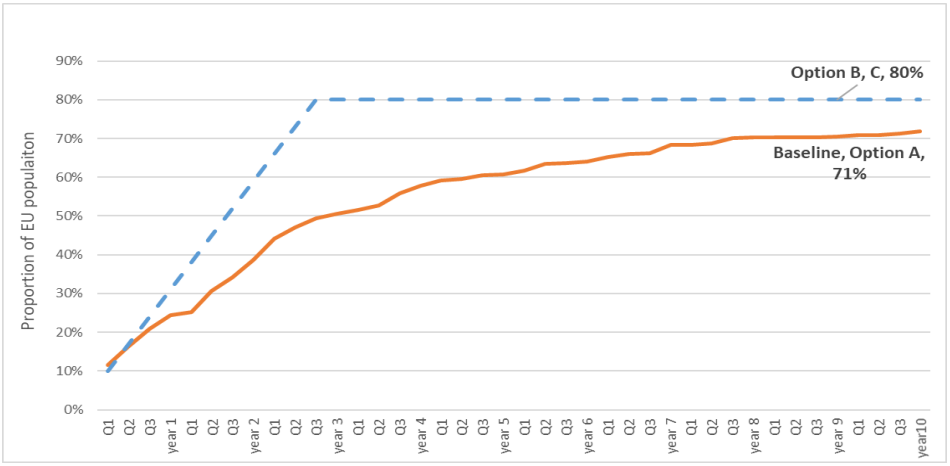


Figure 22 demonstrates the expected impacts of the various policy options on patient access[231]. Option B and C reach a higher plateau of 80% EU population covered, and also much faster than Option A/baseline, two years following authorisation. The maximum achievable access is less than for non-orphan medicines, given the sometimes extremely low or non-existent patient population in Member States. We based our estimation on data from SPC protected orphan medicines, which can reach an average 80% population coverage even in rare conditions, but with higher financial incentives. We assume, that soon after 2 years from authorisation this plateau would be reached, because of the incentive.

7. Medicines for children - Modelling changes in SPC-extension duration

a. Protection types and length in a sample of medicines

In the basket of products from IQVIA database with protection expiry between 2016 and 24, 20% of medicines (40/199) are benefiting either from the +6 months SPC extension (36) or from the two years market exclusivity extension (4) as last protection to expire. These products are highlighted in Figure 6, presented by the length of their overall protection. Importantly, those medicines that are protected by a patent or regulatory protection as a last line of protection (90/199) and not by SPC or market exclusivity, cannot benefit from the reward for carrying out studies in children.

It is important to note that from the IQVIA database it is not possible to determine which products have been studied in children. On the basis of historical data it can be assumed that around 50% of the products under development are granted a full waiver from the obligation of conducting a PIP. By extrapolation, it can be expected that also in the basket considered only 100 of products were subject to the obligation to conduct a PIP. Which brings the percentage of products rewarded with a PIP extension to around 40% of the eligible products.

As explained in the previous section, the number of SPC extensions are smaller than we would expect from the number of new medicines authorised with a PIP obligation, due to a lag in completing PIPs, often many years after authorisation of the adult medicine. Interestingly, medicines with high sales are good at timely completion of the PIPs, we have noted that out of 12 blockbuster medicines (those that have a revenue of €1 billion per year in the EU market) in our basket, 8 had a paediatric extension. In their case, the motivation was high: a 6-month extension generates hundreds

[231] It is hereby important to keep in mind that these incentives work with medicines that are not protected by SPC or patents, as those IP incentives provide longer protection than the maximum achievable market exclusivity for more than half of all newly authorised medicines.

of millions of additional protected revenues. This is reflected in Table 4, those medicines for which the SPC extension is the last layer of protection have longer protection times, and higher average revenues than all the other medicines.

Figure 23 - Distribution of products with paediatric extension by length of protection

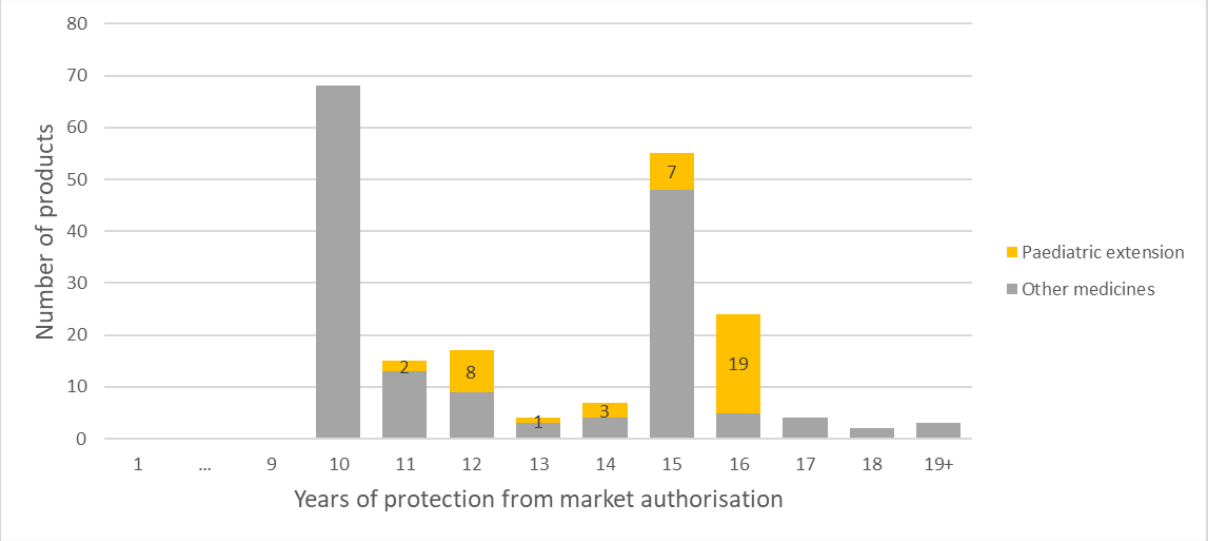


Table 37 - Peak annual sales and protection period of products with paediatric extension

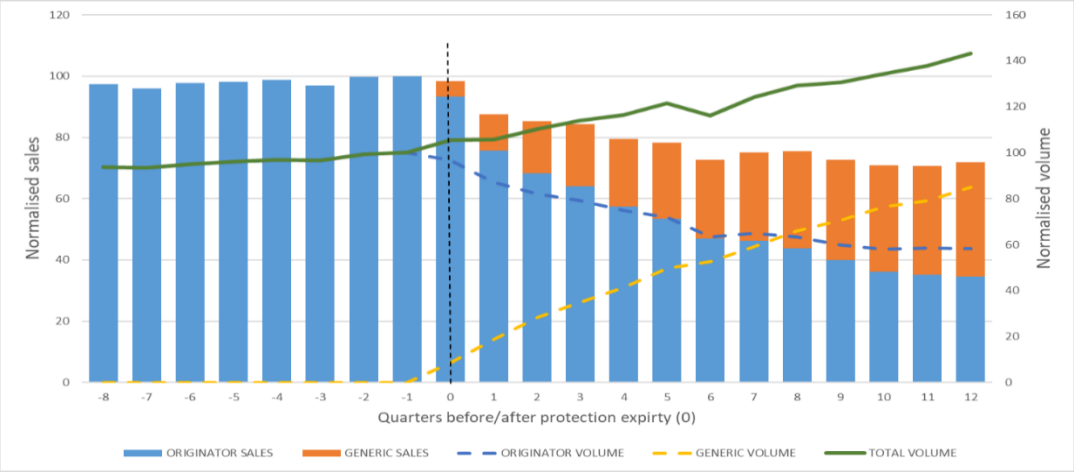
	Avg. peak annual sales	Avg proection period
Paediatric extension	€ 540.6 m	14.3 years
Other medicines	€ 199.5 m	12.7 years

b. Developing an 'analogue' representing an innovative medicinal product lifecycle

To measure the impacts of changes in the SPC extension, we used the same concept as for the general pharma and for the orphan medicines. However, those medicines benefiting from the SPC extension have typically longer protection and generate much higher revenues than the RP protected ones, which serve the basis of the general pharma analogue. The high sales medicines are more prone to generic competition, because of the lucrative market, the generic competitors come faster, in bigger number and with more aggressive price competition.

To properly account for this difference, we built a new analogue based on a different basket of products is used. For this exercise, we considered the 11 products[232] whose SPC protection expired in France, Germany, Italy and Spain between 2016 and 2018 and for which SPC protection is the last line of protection. Since the options concern increases or decreases in protection by six months, quarterly rather than annual data were used.

[232] ADALIMUMAB, BOSENTAN, CASPOFUNGIN, ENTECAVIR, EZETIMIBE, IMATINIB, IVABRADINE, RUPATADINE, TIGECYCLINE, TIOTROPIUM BROMIDE, VORICONAZOLE



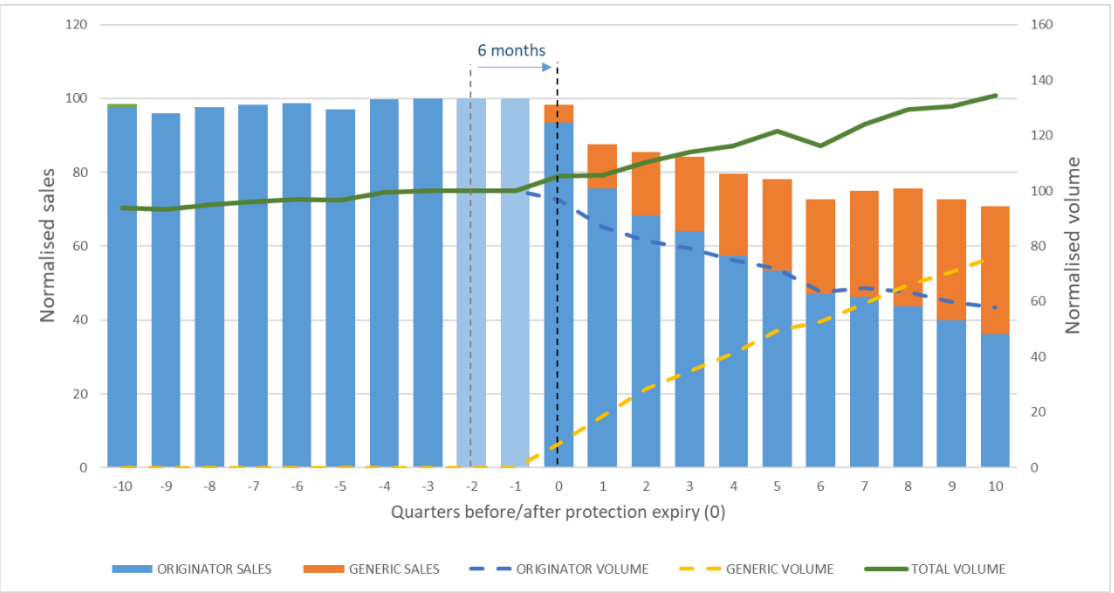
quarter from expiry		-8	-4	-1	0	4	8	12
ORIGINATOR	SALES	97	99	100	93	57	44	35
GENERIC	SALES	0	0	0	5	22	32	37
TOTAL	SALES	97	99	100	98	80	76	72
ORIGINATOR	VOLUME	94	97	100	97	75	63	58
GENERIC	VOLUME	0	0	0	9	41	66	85
TOTAL	VOLUME	94	97	100	105	116	129	143
ORIGINATOR	PRICE	1.04	1.02	1.00	0.97	0.77	0.69	0.59
GENERIC	PRICE				0.56	0.53	0.48	0.44
TOTAL	PRICE	1.04	1.02	1.00	0.93	0.68	0.58	0.50

The analogue indeed confirmed, that for a typical beneficiary of the SPC extension changes from generic entry are more dramatic. 3 years after the expiry, the volume of generic and originator medicines combined has increased by 43% (suggesting 43% more patients being able to benefit from the medicine) and average price halved, compared to quarter -1, the last protected quarter. As in the general pharma, we have modelled changes by moving the expiry point 2 quarters back or ahead within our 21-quarter long observation period.

c. Modelling the economic impact of increasing SPC extension

We use the same data as presented above and assume that after the Q-1 there will be an additional 2 quarters of peak sales protected by a 6-month additional SPC extension. We will use the result of this model to estimate the proportionate effect of the 12-month SPC extension incentive for UMN addressing medicines in Option A. We assume that pre-expiry sales trajectory is unchanged, the market dynamics of generic competition post expiry is unchanged. In the figure below thus data associated with a new Q-1 is added twice and the baseline Q11 and 12 are removed to maintain the overall observation period of 21 quarters. Figure X

Figure 24 - Normalised volume and sales data for products with +2 quarters of SPC extension



	Baseline	12-month SPC ext	change
Originator protected sales	785	985	**+200**
Originator contested sales	695	625	**-70**
Originator gross profit	975	1101	**+125**
Generic sales	327	254	**-73**
Generic gross profit	108	84	**-24**
Cost to public payer	1807	1865	**+58**
Volume (patients served)	2360	2278	**-81**
Cost of baseline volume	1807	1923	116

Note: colour code shows increased benefit/reduced cost (green) or decreased benefit/increased cost (red) to the stakeholder

Using the above model for the product lifetime, we can make the following observations at product level:

- Originator companies increase pre-expiry sales due to additional 6 months of monopoly sales by 200 (normalised units). In terms of gross profit, this is 125 more normalised unit.
- Generic companies' start to benefit from sales 2 quarters later, and thus generic sales are reduced by 73 (normalised units), and gross profit is reduced by 24 (normalised unit) compared to the baseline.
- Healthcare payers pay more overall due to an increase in the average price they need to pay for a standard unit of the product. The total cost for healthcare payers is thus +58 (normalised units) over the product lifetime compared to baseline
- Patients lose -81 (normalised units) in decreased volumes of the medicine over the lifetime of the product compared to baseline.

i. Monetising the systemic effects of 12-month SPC extension for medicines addressing UMN (Option A)

We expect that 20% of the new products will meet the UMN criteria, therefore out of the expected yearly 10 SPC extension, 2 would be for UMN addressing medicine. Increasing the current 6-month

SPC extension to 12 for these medicines would result in the following impacts, by using the changes values of the models and the value of €540 m peak annual sales, derived from historic data.

Table 38 - Impact of 6 months protection increase (+12 months SPC extension) for UMN on different stakeholders

	avg product (€540 m annual sales)	Systemic impact (2 extensions/year)
Originator gross profit	**+€169 m**	**+€338 m**
Generic gross profit	-€32 m	-€64 m
Public payer's gain/loss (cash)	-€78 m	-€156 m
Δ of patients treated (monetised)	-€78 m	-€156 m
Patient and payer gain/loss	**-€156 m**	**-€312 m**

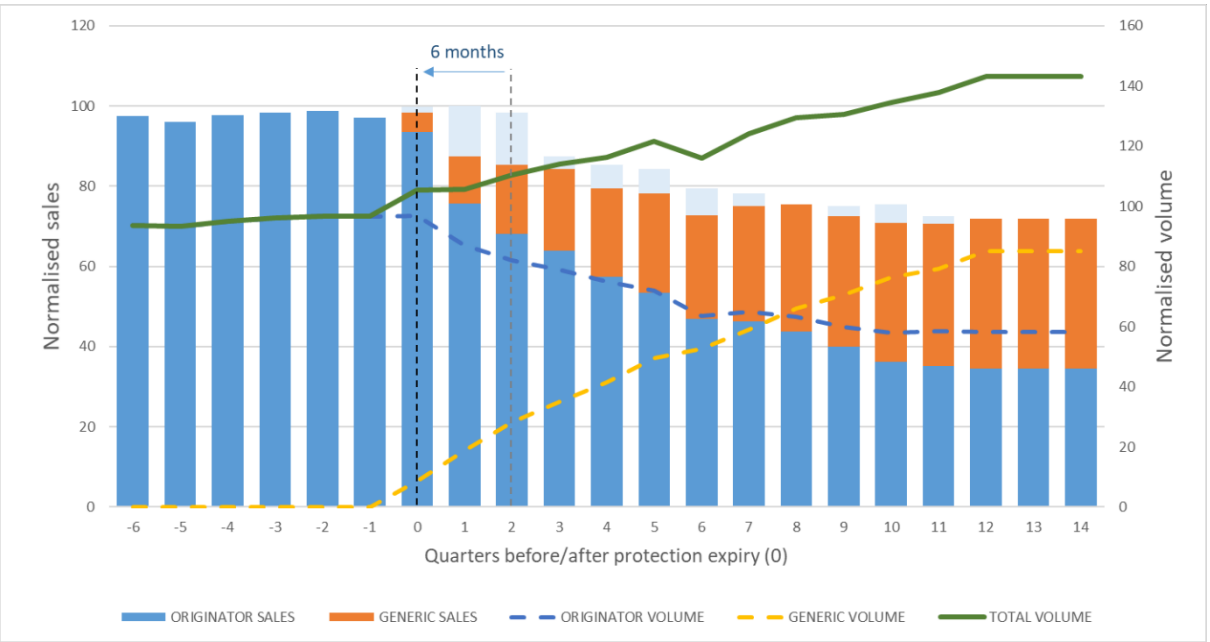
Thus, benefiting originator companies would increase profits by €338 m at a cost of €312 m to the public. Generic companies would experience a €64 m decrease in their gross profits.

d. Modelling the economic impact of decreasing SPC extension

Option B would abolish SPC extension reward, thus reducing protection by 6 months compared to the baseline. This will be the new scenario for the analogue. In the model, we assume that after 3 full years of generic competition an equilibrium value of annual sales and volume of product sold are established and thus we can use Q12 data for originator and generic products as long-term level to calculate the value of ME loss over the product lifetime.

We also assume that the pre-expiry sales trajectory is not changed by company behaviour and thus the baseline Q-1 and Q-2 sales are lost under the new regime. In the figure below thus the original Q-1 and Q-2 values are removed and Q13 and Q14 values are added at equilibrium level. In addition, we assume that the market dynamics of generic competition (between Q0 and Q12) in the new regime will not change compared with the baseline 6-month SPC extension.

Figure 25 - Normalised volume and sales data for products with -2 quarters of SPC extension



	Baseline	No SPC	change
Originator protected sales	785	585	**-200**
Originator contested sales	695	764	**+69**
Originator gross profit	975	850	**-125**
Generic sales	327	402	**+75**
Generic gross profit	108	133	**+25**
Cost to public payer	1807	1751	**-56**
Volume (patients served)	2360	2447	**+87**
Cost of baseline volume	1807	1695	-112

Using the above model we can make the following observations at product level:

- Originator companies' pre-expiry sales loss of -200 (normalised units) translates to a decrease in originator's gross profit of -125 (normalised units) over the observed 21-quarter period.

  We know that pharmaceutical industry is one of the most R&D intensive sector and they reinvest a large share of their revenue into innovation for new products and technologies. This share is 20% on average globally[233] and we can assume that the revenue loss will translate to a loss of innovation budget.

- Generic companies' start to benefit from sales half year earlier compared to baseline, and thus reach equilibrium level 2 quarters earlier. These two extra quarters of equilibrium generic sales of +75 (normalised units) are equal to +25 (normalised units) gross profit gains.
- Healthcare payers pay less overall due to a decrease in the average price they need to pay for a standard unit of the product. In the baseline +6 months SPC extension regime, the total lifetime

[233] See https://www.drugdiscoverytrends.com/pharmas-top-20-rd-spenders-in-2021/

sales is 1807 (normalised units) and in the new 8-year protection regime the same volume at the new prices would be 1756 (normalised units). Thus in the new situation healthcare payers would pay 56 (normalised units) less.

In the real situation, however, healthcare payers may not realise this nominal saving but choose to purchase more units of the medicine at a lower price for the healthcare system and expand coverage of patients. The difference in the cost of the baseline volume (at new prices) contains both the decreased payment and the extra volumes, so the joint gain for the public is 112 (normalised unit).

- Patients benefit due to the increased volume of the medicine sold after protection expiry (6 months earlier) which then reach more patients creating higher level of health benefits. In the model, the total volume increases as soon as generic products enter the market and volume of generic products surpasses that of the originator product by year 4 after generic entry. In the new regime the total volume sold increases by +87 (normalised units).

i. Monetising the systemic effects of abolishing SPC extension (Option B)

Under option B, medicines which would currently be eligible for the 6-months SPC extension will lose such protection. Generic medicines could enter the market earlier and public authorities would pay less, for more patients served. We have adjusted our model to the new expiry and compared it to the baseline. Table 38 shows the impact of the change for all stakeholders, both at an individual product level, and at systemic level for all 10 products, that would benefit from the extension in the baseline.

Table 39 - Impact of 6 months protection reduction on different stakeholders

	avg product (€540 m annual sales)	Systemic impact (10 extensions/year)
Originator gross profit	**-€169 m**	**-€1,690 m**
Generic gross profit	+€33 m	+€330 m
Public payer's gain/loss	+€76 m	+€760 m
Δ of patients treated (monetised)	+€75 m	+€750 m
Patient and payer gain/loss	**+€151 m**	**+€1,510 m**

At an individual product level, the reduction is a significant loss to the **originator company**, an average SPC extended product would lose -€169 m gross profit. The **generic** products would have +€33 m higher profits thanks to the earlier entry. The **public payer** would experience +€76 m yearly savings, however this is not the only benefit for the public. Not only the total cost would be less, but more **patients** could be served with the more affordable medicine, adding an additional +€75 m monetised patient benefit. Overall the public gains €151 m thanks to the reduction. Looking at systemic level, the loss of 10 SPC extensions compared to the baseline would cause €1.690 m profit loss to the innovator industry annually. On the other hand, the public would make significant savings, to the tune of €1,510 m per year.

e. Cost of a PIP

Building on data reported in the Joint Evaluation Table 7, which provides the probability that each cost is incurred during the conduction of a PIP, it has been estimated the average administrative (0.5 M€) and R&D (22.2 M€) costs of a completed PIP.

TABLE 40 - Estimated costs of a PIP

Estimated costs of a PIP broken down to stages	*est. avg cost of a PIP stage (EURO)*	*Estimated to happen in PIPs*	*est. avg cost of a completed PIP (EURO)*
Preparation of the initial PIP application	400,000	100%	400,000
Annual reporting and further PIP modifications	100,000	55%	55,000
Other administrative costs	200,000	42%	84,000
estimated AVG administrative cost per completed PIP			**539,000**
In vitro studies and animal studies	800,000	40%	320,000
Development of a paediatric formulation	1,600,000	47%	752,000
Phase II paediatric clinical trials	7,300,000	48%	3,504,000
Phase III paediatric clinical trials	15,700,000	72%	11,304,000
Other R&D costs	14,400,000	44%	6,336,000
estimated AVG R&D cost per completed PIP			**22,216,000**

Source: calculation on data collected from the Joint Evaluation

To estimate the total administrative costs incurred yearly by industries, we have multiplied the number of PIPs completed per year with the estimated AVG administrative cost per completed PIP (539 k€).

The completion of a PIP requires time, the analysis – conducted on 205 pMPs with a PIPs agreed during 2007-2020 – of the time needed to obtain a market authorisation (MA) for the paediatric indication after the completion of the PIP, identified an average time of 5.3 years – rounded to 5 - from the first EMA opinion to the MA date[234] (information on both dates are available for 119 of the 205 pMPs, 58%), in line with the 7 years of the "average planned duration of a PIP, from the date of initial application to the planned completion date" reported in the Joint Evaluation. Therefore, it was assumed that R&D costs of a PIP (22.2 M€) are equally distributed over the 5-year period preceding the MA (year of obtainment included) to estimate the total R&D costs incurred yearly by industries

ANNEX 5: HOW OPTIONS ARE EXPECTED TO CONTRIBUTE TO THE ACHIEVEMENT OF THE OBJECTIVES

1. Options for rare diseases

Objective	Common elements	PO A	PO B	PO C[235]

[234] It has been observed that "*The median time to the composite endpoint of first results reporting (either in a trial registry or peer-reviewed journal) was 4.7 years (IQR 3.2 to 5.8 years) from the date of publication of the PIP*" [Hwang, T. J., Tomasi, P. A., & Bourgeois, F. T. (2018). Delays in completion and results reporting of clinical trials under the Paediatric Regulation in the European Union: A cohort study. PLoS medicine, 15(3), e1002520. https://doi.org/10.1371/journal.pmed.1002520].

[235] All the options (PO A, PO B and PO C) include also common elements. Common elements are presented separately only once to facilitate presentation and avoid repetitions.

1. Foster innovation and investment in research and development of medicines for rare diseases and for children especially in areas of (high) unmet medical need	Criteria to identify products addressing HUMN will be set in the Orphan Regulation. Products addressing HUMN will be entitled to increased scientific support by the Agency. *These measures are expected to facilitate the development and faster development of products addressing HUMN*	10 years of market exclusivity (ME) + transferable regulatory protection voucher for HUMN products *The 10–year market exclusivity (the same for all orphan products categories) will foster the development of research into orphans in general, hence contributing to innovation. It is the transferrable regulatory protection voucher (granted to products addressing HUMN) which is expected to foster research into HUMN (and hence also more targeted innovation)*		Variable duration of the ME: 10 years of ME for HUMN products; 9 years of ME for new active substances; 5 years of ME for well-established use products. *While the market exclusivity targets all orphan products, a modulated duration of ME will better direct research into HUMN and into new active substances.*
2. Create a more balanced and competitive system that keeps medicines affordable for health systems and patients while rewarding innovation	Generics/biosimilars can enter the market at day-1 of the expiry of the exclusivity period by allowing the filing of an application prior to expiry. *This measures aims at a faster entry of cheaper generics (affordability), which at the moment is delayed by the time needed from filing of the application until granting an authorisation (120 days). At the same time, the measure does not impact innovation, as the ME period remains intact.* Reduction of consecutive periods of market exclusivity for new indications of the same orphan medicine by introducing them under the same "Global Marketing Authorisation" (GMA). *This measure, by proving the extension of ME for only two first new indications, will allow (cheaper) generics to enter*		No ME *No ME exclusivity will ease the entry of generics, but at the same time, it may be questioned whether innovation will be sufficiently rewarded.*	Variable duration of the ME *This measure will create a more balanced system where especially innovation and addressing HUMN is rewarded. Authorisation of orphan products with well-established use will still be rewarded (as it is important to have products officially authorised for a specific use on the market), but with a shorter 5-year ME. Variable duration of ME will help faster entry of generics (to address affordability).*

	faster the market (affordability). At the same time, it creates a better balance between the need to reward innovation (while avoiding unjustified benefitting from the system|) and the need for a fast generics entry, The market exclusivity granted to a second generation product that is similar to the first generation product shall not be applied in respect of generic products of the first reference product for which the market exclusivity expired. *As above, this measure preserves innovation and blocks the unjustified benefiting from the system of incentives ('evergreening'), while allowing a faster entry of generics (affordability).*			
3. Enable timely patient access to orphan and paediatric medicines in all Member States	Generics/biosimilars can enter the market at day-1 of the expiry of the exclusivity period by allowing the filing of an application prior to expiry. *This measure ensures timely access of generics. See also explanations for this measure in point 2.* Reduction of consecutive periods of market exclusivity for new indications of the same orphan medicine by introducing them under the same "Global Marketing Authorisation" (GMA). *This measure*			Extension of the ME if market launch in all EU Member States (for HUMN products and new active substances). *This measure awards those companies which made efforts to reach out to all MS, even those where marketing products is less attractive for companies (due to limited public funds to buy expensive medicines, small markets, etc.)*

	ensures timely access generics. See also explanations for this measure in point 2. . The market exclusivity granted to a second generation product that is similar to the first generation product shall not be applied in respect of generic products of the first reference product for which the market exclusivity expired. *This measure ensures timely access generics. See also explanations for this measure in point 2.* Encourage companies that lose the commercial interest in an orphan medicine to offer it for transfer to another company rather than withdrawing it *This measure will help patients' access to a medicine which risks withdrawal from the market.* The duration of the orphan designation (assigned early in the development of a product and prior to obtaining a marketing authorisation) will be capped for newly designated orphan medicinal products at 7 years. *This measure is expected to motivate the sponsor to timely develop the product and as a result it helps timely patients' access.*			
4. Reduce the regulatory burden and provide a flexible regulatory framework.	Provide for the possibility to adapt the current definition of an orphan condition *This measure opens up the possibility that the current*			

	definition of an orphan condition may be easier adapted (for example to scientific developments). The orphan designation criterion on the basis of return on investment will be deleted. *This measure 'cleans up' a criterion to get an orphan designation that has become obsolete.* Responsibility for adopting decisions on 'orphan designations' will be transferred from the Commission to the Agency. *This measure will facilitate and expedite the procedure, as the same body (Agency) will be responsible for a scientific opinion and for an orphan designation (while currently the Commission gives the decision on an orphan designation).*			

Further explanation of important parts of the common elements:

- ***Global marketing authorisation*** (*Reduction of consecutive periods of market exclusivity for new indications of the same orphan medicine by introducing them under the same "Global Marketing Authorisation" (GMA).*

'Global marketing authorisation' is a concept which exists already under Directive 2001/83/EC (Article 6(1)) and means that a medicinal product has been granted a marketing authorisation, any additional strengths, pharmaceutical forms, administration routes, presentations, as well as any variations and extensions shall also be granted an authorisation in accordance with the first subparagraph or be included in the initial marketing authorisation. All these marketing authorisations shall be considered as belonging to the same global marketing authorisation. A measure proposed in this IA under the Orphan Regulation uses the same concept, but for the purpose of indications as one medicinal product may have a several indications (an indication means a medical condition that a medicine is used for. This can include the treatment, prevention and

diagnosis of a disease[236]). An indication should clearly state the disease/condition and population that a medicine is intended to treat. What is taken into account is severity of the disease, the place in the therapy, e.g. 1st, 2nd line, use in the combination therapy and other[237]. As these indications may be formulated narrowly, the measure of reduction of ME, which would be granted only for two indications, prevents drawing unjustified benefit from the ME.

- ***Transfer of the orphan marketing authorisation*** (*Encourage companies that lose the commercial interest in an orphan medicine to offer it for transfer to another company rather than withdrawing it*)

At the moment companies which lose the commercial interest in an orphan medicine may withdraw it from the market with no regulatory consequences, while generic products will not necessarily be interested to fill in the gap, either (rare diseases are characterised by very small patient populations). Even if another company would be willing to take over, the fact of withdrawal may be not sufficiently publicised and other forms of encouragement not provided.

- ***Duration of orphan designation*** (*The duration of the orphan designation (assigned early in the development of a product and prior to obtaining a marketing authorisation) will be capped for newly designated orphan medicinal products at 7 years)*

Currently, the orphan designation once granted is not limited in time. There may be situations where the orphan designation is lost (see Article 5 (12) of the Orphan Regulation)[238], but the lapse of time is not one of them. Several orphan designations may be introduced to the Register of Orphan Medicinal Products for the same condition, all of them entitled to pre-authorisation scientific and procedural facilitations, so one designation does not block research on other products. However, as the ultimate purpose is to deliver the product to the patient, companies should be encouraged to swiftly proceed to the marketing authorisation stage. The overpopulation of the Register with 'old' designations is also not good for its readability. As the average time the average time between orphan designation and MA Application (MAA) is 5 years, a somehow longer period of seven years, was suggested for a cap.

- ***Designation procedure*** (*Responsibility for adopting decisions on 'orphan designations' will be transferred from the Commission to the Agency.)*

The procedure for designation is set out in Article 5 of the Orphan Regulation. The applications for orphan designation are examined by the EMA's Committee for Orphan Medicinal Products (COMP), using the network of experts that the Committee has built up. The evaluation process takes a maximum of 90 days from validation. The Agency sends the COMP opinion to the European Commission, which is responsible for adopting a decision on the orphan designation within 30 days of receipt of the opinion. The full list of orphan designations is available in the Community register of orphan medicinal products for human use, managed by the Commission. In the proposed change, the responsibility for adopting decisions would be transferred to the Agency, which is expected not make the procedure faster and less burdensome.

[236] Indication | European Medicines Agency (europa.eu)
[237] Wording of therapeutic indication - guide for assessors (europa.eu)
[238] (a) at the request of the sponsor; (b) if it is established before the market authorisation is granted that the criteria laid down in Article 3 are no longer met in respect of the medicinal product concerned; (c) at the end of the period of market exclusivity as laid down in Article 8.

2. Options for medicines for children

Objective	Elements common to all PO	PO A (SPC extension and novel incentives for UMN products)	PO B (No SPC extension)	PO C[239] (6 months SPC extension)
1. Foster innovation and investment in research and development of medicines for rare diseases and for children especially in areas of unmet need.	Criteria to identify products which have the potential to address unmet medical need of children will be defined in the general pharmaceutical legislation. Products which respond to these criteria will be entitled to increased scientific support by the Agency in the early phases of development this will help the development of novel products for children in areas of UMN. This measure is expected to benefit in particular SME who have more limited resources than big pharma companies Review of the waiver system to take into account the mechanism of action of a product: For products which, on the basis of scientific evidence on the mechanism of action, could also be effective against a different disease in children, clinical studies in children will have to be conducted. This will results in novel products for children in particular in areas in areas of UMN The new procedural system will allow for evolutionary PIP, which will help accommodate innovation	Novel incentives for UMN products. alternatively: A regulatory protection voucher (duration 1 year) or an extra 12 extra months SPC extension (on top pf 6 months' extension for all medicinal products) The novel incentives are expected to support the development of novel products for children in the areas of UMN		
2. Create a more balanced and competitive system that keeps medicines affordable for health	Abolishing the market exclusivity extension for completing PIPs would regulate a system that is not functioning well and		The abolition of the SPC extension will allow earlier generic entry and consequently	

[239] All the options (POA, POB and POC) include also common elements. Common elements are presented separately only to facilitate presentation and avoid repetitions.

systems and patients while rewarding innovation ;	will allow predictability for generic products and faster entry of generics in cases where products are not orphan medicines (which in turn will affordability due to lower prices of generics)		improve affordability for the health systems	
3. Enable timely patient access to orphan and paediatric medicines in all Member States;	Cap the duration of the deferrals to 5 years allowing faster development of medicines for children and consequently a higher access to them. The procedure for setting out a PIP will be streamlined and simplified allowing for quicker completion of the PIP and faster authorisation allowing a faster access to new medicines for children Abolishing the market exclusivity extension for completing PIPs would regulate a system that is not functioning well and will allow predictability for generic products and faster entry of generics in cases where products are not orphan medicines		No SPC extension will ensure a faster access to generic product	
4. Reduce the regulatory burden and provide a flexible regulatory framework.	Introduction of an evolutionary PIP model for specific paediatric developments Introduction of an simplified PIP model for specific paediatric developments) These measures are expected in resulting in reduced administrative costs for companies.			

Common elements:

- *Evolutionary PIP*

In the current legislation a complete development plan needs to be submitted to the Agency and agreed with at very early stage of development (after the completion of the pharmacokinetic and pharmacodynamics studies). For certain type of development this is problematic. For example when a molecules have never been used before, the detailed design of the each step of clinical development depends from the results obtained in the previous studies. The obligation to submit a full development plan at early stages obliges developers to make assumptions on the results that will be obtained in the future and results in subsequent need to modify the development plan (PIP) several times. This create delays in the completion of the PIP and administrative burden for the applicants and for the Agency.

With the concept of evolutionary PIP, certain type of developments, like molecules used for the first type in human, will be given the possibility to present a high level clinical development plan. The Agency will agree that the development plan will be completed and new information submitted and agreed at precise development steps. This will reduce the administrative burden and create when necessary a more agile PIP system.

- *Simplified PIP*

The PIP system has been put in place taking into account the development of products for adults for which a clinical development in children derives from the obligation imposed by the legislation.

However, there are cases, like paediatric only products or PUMA products which are developed specifically for children and would therefore be developed indipendedly from the paediatric Regulation. For these products the binding elements and the details that have to be presented in a PIP can be lowered. Specific guidelines on the elements that will be requested for this category of products will be determined by the Agency in close collaboration with interested stakeholders and the Commission.

- *Changes to the waiver system to take into account the mechanism of action of a product*

Currently, the obligation to conduct a PIP in children is waived in certain situation, for example when an adult product is intended for a disease not existing in children.

However, in certain cases the molecule in question, due to its molecular mechanism of action may be efficacious against a disease in children different from the one for which it was initially designed for use by adults. For example a product developed to treat an adult cancer, non-existing in children, could also be effective to treat a different type of cancer in children.

The waiver system is intended to be amended in order to oblige the conduct of PIP also when on the basis of the molecule of action of the product, it may treat a different disease in children.

A similar system has recently been introduced in the US[240].

- *Cap to the length of deferrals*

While the paediatric legislation foresees that clinical studies in children should be completed before the marketing authorisation in adult is granted, there is the possibility *to defer* the completion of some PIP studies only after the marketing authorisation of an adult product. It is envisaged to cap the maximum length of this derogation to 5 years, so that products reach children quicker than today.

- *Abolish the paediatric market exclusivity extension*

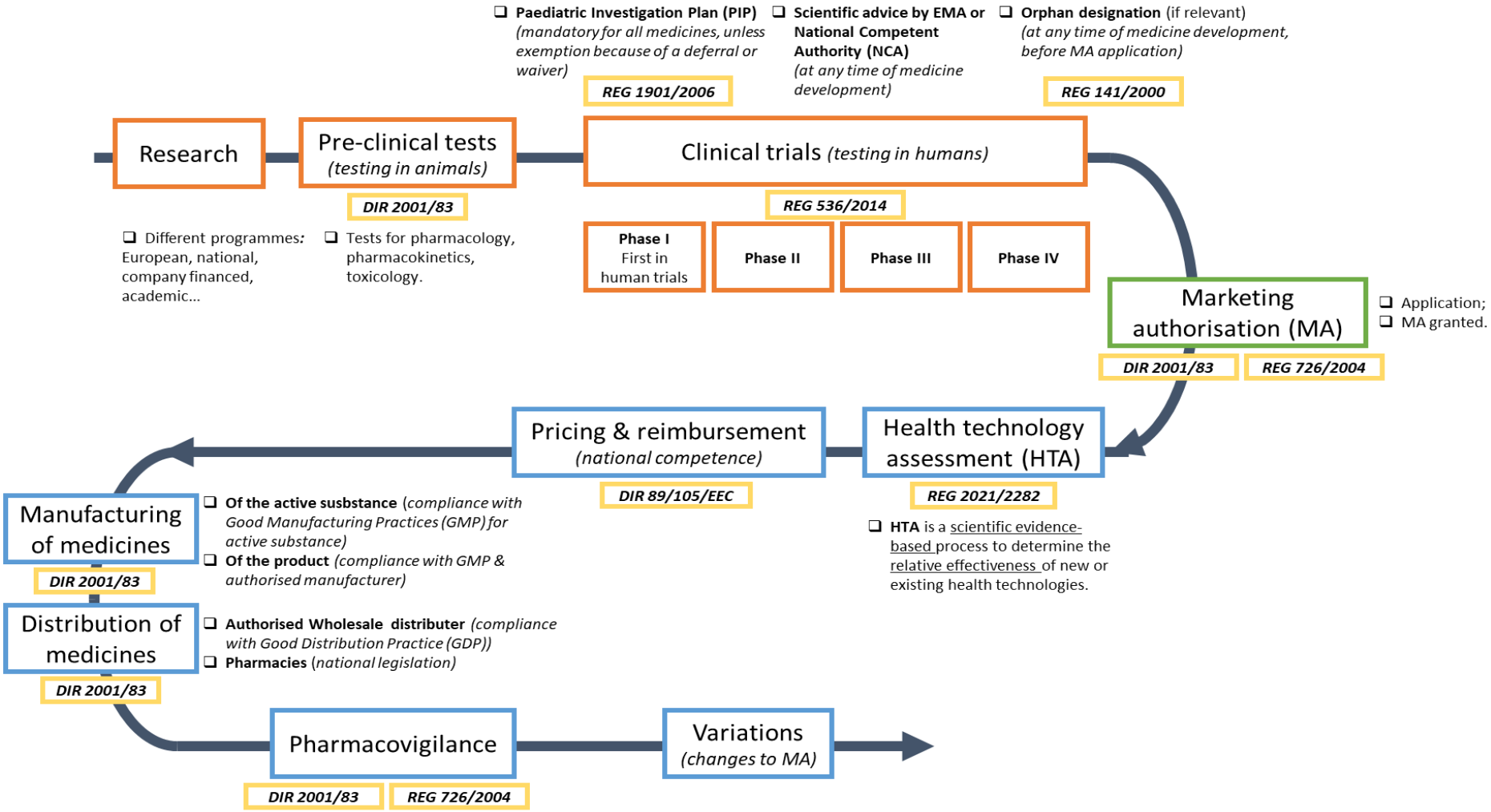
This measure intends to regulate a dysfunctional system. Currently the paediatric regulation offers 6 months SPC extension for completing PIP, and for orphan medicines 2 years of market exclusivity extension. From the entry into force of the Paediatric Regulation up to 2020, only 11 of these market exclusivity extensions were granted. The system has allowed some companies to game the system: there have been cases where companies have abandoned the orphan status of their product at the moment of marketing authorisation in order to benefit from the 6 months SPC extension. This has made difficult for generic products to know exactly when the paediatric protection would expire and consequently to plan accordingly.

- *Facilitations for products addressing UMN*

[240] Download (fda.gov)

Criteria to identify products which have the potential to address unmet medical need of children will be defined in the general pharmaceutical legislation. Products which respond to these criteria will be entitled to increased scientific support by the Agency in the early phases of development and dedicated funding.

ANNEX 6: VISUAL OVERVIEW OF THE LIFE-CYCLE OF A MEDICINAL PRODUCT INCLUDING LINKS TO LEGAL FRAMEWORK



ANNEX 7: OVERVIEW OF ECOSYSTEM AND LEGAL FRAMEWORK

1. The pharmaceutical ecosystem

1.1. General

The Pharmaceutical Strategy for Europe[241] describes the pharmaceutical ecosystem and changes in the landscape that transform industry and medicines development from the old model of chemical blockbuster medicines to biological medicines, advanced therapy medicines, combined medicines with software and personalised medicines. Health data is key to fully exploiting the huge potential of new technologies and digitisation. This vision is echoed in the health ecosystem of the updated European industrial strategy[242].

The EU pharmaceutical ecosystem covers activities from pre-clinical research to manufacturing and includes actors ranging from manufacturers (including medical devices and equipment and personal protective equipment), healthcare services; health tech and related services[243]. Overall, it covers **24.8 million direct jobs**, **493 000 firms** (including 99.7% SMEs) and contributes to **9.5% of EU value added**[244]. The EU provides an attractive market for the pharmaceutical industry, especially with regards to the activities and support provided by the European Medicines Agency and the EU-wide marketing authorisation. These elements are key in attracting R&D to the EU and are regulated by the general pharmaceutical legislation. At global level, the EU health industries are also key players in competition with North America and Asia. As an example, in 2018, North America accounted for 48.9% of global sales of medicines compared to Europe (incl. Switzerland) accounting for 23.2%. The EU also accounts for 24% of the world's API production compared to 65.5% being produced in Asia Pacific. The EU pioneered in sophisticated biologic innovative medicines (and biosimilar medicines), however, Asia and the US are rapidly catching up[245].

In the ecosystem, 'big pharma'[246] are increasingly outsoucing functions, including clinical trials and manufacturing, and are focusing investment on a limited number of therapeutic areas while disinvesting from others[247]. Emerging biopharma companies – often SMEs – are driving a large portion of innovation and development. Emerging biopharma companies were responsible for a record 65% of the molecules in the R&D pipeline in 2021, up from less than 50% in 2016 and 33% in 2001. Top pharmaceutical companies' share of the total R&D pipeline has been shrinking over the last decade (PharmaProjects 2020).

Big pharma is increasingly disinvesting from risker upstream research and instead access products that are already in later clinical trials stages through acquisitions of small biotech

[241] COM(2020) 761 final.
[242] COM(2021) 350 final European industrial strategy | European Commission (europa.eu).
[243] SWD(2021) 351 final – page 138.
[244] SWD(2021) 351 final – page 137.
[245] SWD(2021)351 final – page 139.
[246] Understood as multinational companies dominating the industry sales and traditionally responsible for all aspects of the medicines discovery pipeline.
[247] European pharmaceutical research and development. STUDY Panel for the Future of Science and Technology. European Parliament Research Service.

companies or start-ups with promising portfolios of patents[248]. Once the molecule reaches a certain maturity (e.g. completing phase II clinical trials) and still looks commercially promising, big pharma companies come in, they partner, buy the molecule or buy the company at the stage of the expensive late-stage clinical trials, marketing authorisation and market launch. Licensing is also used extensively in the pharmaceutical sector, though small firms and start-ups also rely on venture capital to finance their R&D (Kyle 2020).

2. Legal framework

a. Basic legislative acts

The **general EU pharmaceutical legislation** consists of Directive 2001/83/EC and Regulation (EU) No 726/2004 forming one policy intervention. Directive 2001/83/EC provides the framework for authorisation and monitoring of medicines post-authorisation (pharmacovigilance) for nationally authorised medicines, manufacturing and wholesale distribution and authorisation of actors in the supply chain, advertising and falsified medicines. The Regulation establishes the European Medicines Agency and its governance and provides also the framework for authorisation of medicines through a centralised procedure and for pharmacovigilance of these medicines. When it comes to technical requirements for the authorisation application and the lifecycle management of medicines, the Regulation refers regularly to the common requirements in Directive 2001/83/EC.

Medicines may either be authorised centrally by the Commission based on a positive scientific assessment by the European Medicines Agency (EMA), the centralised procedure (CP), or nationally by an individual or a group of Member States. A medicinal product authorised via the CP is not necessarily accessible in all Member States, as its actual placing on the market may depend on the launch strategy of companies and national pricing and reimbursement decisions. Both legal acts are grounded on the fundamental principle that a medicine for human use may only be placed on the market once authorised based on a positive benefit-risk of its quality, safety and efficacy, and that applies regardless of the authorisation procedure.

The specialised legislations for rare diseases and children ("the Orphan and Paediatric Regulations") complement the general EU pharmaceutical legislation (that also apply to medicines for rare diseases and children) to specifically support the development in these previously neglected areas, mainly through specific, additional incentives and obligations. Both the Orphan and Paediatric Regulations are designed to address specific unmet medical

[248] European pharmaceutical research and development. STUDY Panel for the Future of Science and Technology. European Parliament Research Service.

needs of small populations: (i) the Orphan Regulation aims at enabling research, development and authorisation of new medicines for rare diseases through specific incentives and (ii) the Paediatric Regulation works mainly with obligations. It compels companies already developing products for adults to screen them for possible use in children. It provides rewards once this obligation has been fulfilled, to compensate for the additional costs.

The revision of these specialised legislations, also ongoing, follows coherent objectives with the revision of the general pharmaceutical legislation: promoting innovation to better address unmet medical needs, ensuring access of patients to innovative medicines and reducing regulatory burden. Taken together, they aim to ensure the right balance between giving incentives for innovation to strengthen the research base of the EU pharmaceutical industry and the need for patients to have access to affordable medicines.

Advanced therapy medicines[249] are also regulated under specialised legislation. This legislation is also an 'add-on' the general pharmaceutical legislation for this specific product category and concerns in particular technical requirements adapted to the particular characteristics of these products, special incentives for SMEs and their assessment. The legislation on advanced therapy medicines is not subject to revision and as such not in the scope of this impact assessment.

These legislations are complemented by more specific ones, applicable at different stages of the lifecycle of medicines.

b. Other legislative acts and policies applicable to medicinal products

i. At the research and development stage

The Regulation on clinical trials[28] harmonises the processes for the assessment and supervision of clinical trials throughout the EU. The evaluation, authorisation and supervision of clinical trials are the responsibilities of Member States and the Regulation ensures harmonisation. The regulation also allows as of 2022 a more efficient process for the approval of multinational trials. Having a single application and a single package will streamline the registration, assessment and supervision processes for EU clinical trials. This will also facilitate the conduct of trials in small populations scattered in several countries.

[249] Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004, OJ L 321, 10.12.2007, p. 121, LexUriServ.do (europa.eu).

The **proposed Regulation on the European Health Data Space** (EHDS)[250] will provide a common framework across EU Member States for access to quality health data for use in research and development of new treatments.

The **European innovation Council** (EIC)[251] established under the Horizon 2020 programme aims at identifying and supporting breakthrough technologies and game changing innovations with the potential to scale up internationally and become market leaders. It supports all stages of innovation from R&D on the scientific underpinnings of breakthrough technologies, to validation and demonstration of breakthrough technologies and innovations to meet real world needs, to the development and scaling up of start-ups and small and medium-sized enterprises (SMEs).

The **Innovative Health Initiative Joint Undertaking**[252] (IHI JU) is a public-private partnership between the European Union, represented by the European Commission, and several health industries from the biopharmaceutical, biotechnology and medical technology sectors. IHI brings together diverse stakeholders (universities, companies large and small, and other health stakeholders) in collaborative projects that address disease areas where there is a high burden on patients and/or society. The initiative focuses on cross-sectoral projects supporting the development of safe, effective, people-centred and cost-effective products and services that target key unmet public health needs.

ii. At the authorisation stage

The authorisation procedures are laid down in the general pharmaceutical legislation but aspects linked to authorisation are completed by other regulations.

Beyond the **general patent rules** applicable to medicines, the **Regulations on supplementary protection certificates (SPCs)**[253] provide for supplementary intellectual property rights extending patent protection for specific medicines. SPCs aim to offset the loss of patent protection for medicines that occurs due to the compulsory lengthy testing and clinical trials these products require prior to obtaining marketing authorisation.

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[250] Proposal for a Regulation of the European Parliament and of the Council on the European Health Data Space, COM(2022) 197 final, Proposal for a regulation - The European Health Data Space (europa.eu).

[251] For more details, see https://eic.ec.europa.eu.

[252] Council Regulation (EU) 2021/2085 of 19 November 2021 establishing the Joint Undertakings under Horizon Europe and repealing Regulations (EC) No 219/2007, (EU) No 557/2014, (EU) No 558/2014, (EU) No 559/2014, (EU) No 560/2014, (EU) No 561/2014 and (EU) No 642/2014, OJ L 427, 30.11.2021, p. 17, EUR-Lex - 32021R2085 - EN - EUR-Lex (europa.eu)

[253] Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the supplementary protection certificate for medicinal products, OJ L 152, 16.6.2009, p. 1, EUR-Lex - 32009R0469 - EN - EUR-Lex (europa.eu) and Regulation (EU) 2019/933 of the European Parliament and of the Council of 20 May 2019 amending Regulation (EC) No 469/2009 concerning the supplementary protection certificate for medicinal products, OJ L 153, 11.6.2019, p. 1, EUR-Lex - 32019R0933 - EN - EUR-Lex (europa.eu).

Table 41 - Overview of the current IP and regulatory protection incentives for medicines

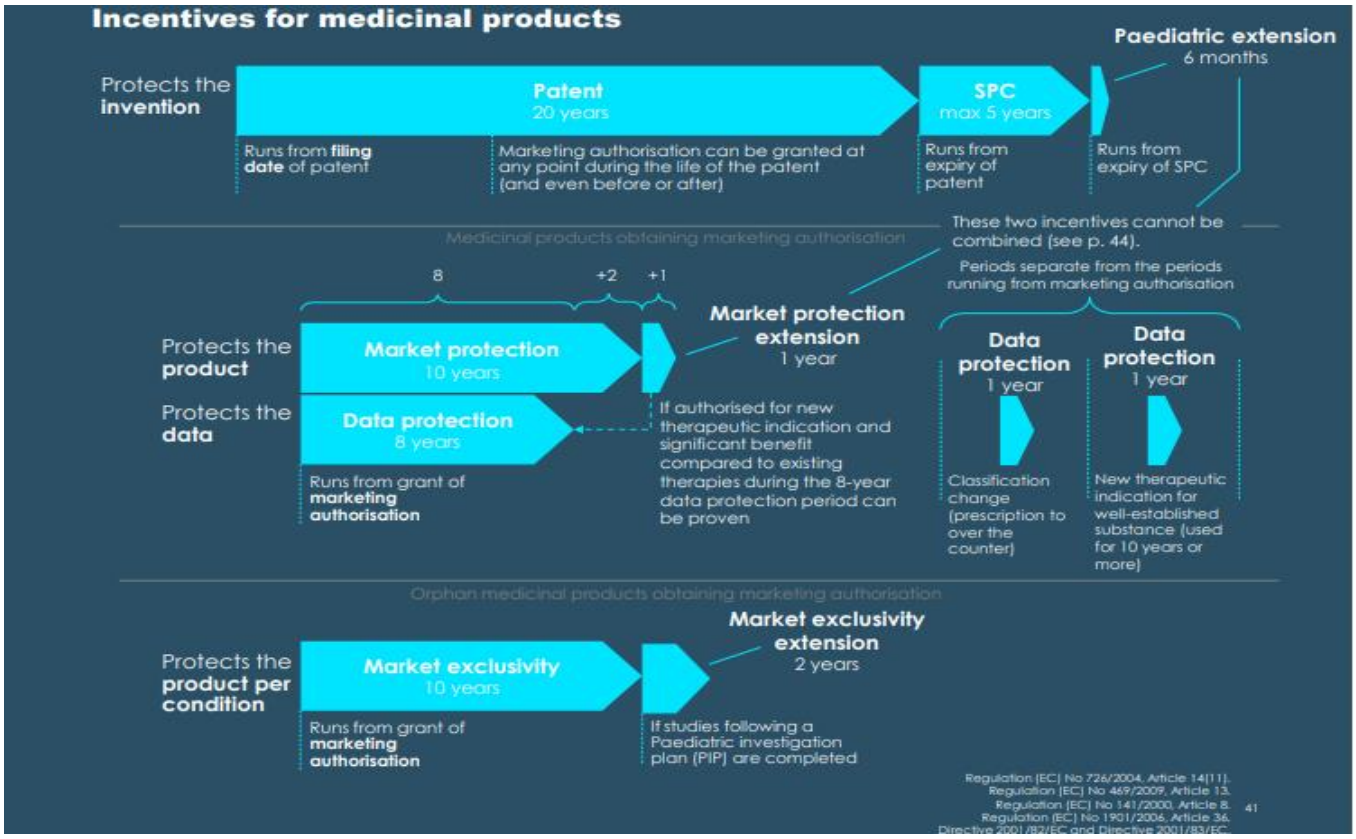

Table 41 above provides an overview[254] of the current IP and regulatory protection rules for medicines in the EU.

The ongoing review of the SPC regulation[255] will put in place a unitary SPC and/or a single ('unified') procedure for granting national SPCs. This will make SPCs more accessible and efficient, and will impact the health sector.

iii. At the market launch stage

Following marketing authorisation companies take decisions on the market launch in Member States based on commercial considerations[256]. These decisions are influenced by the

[254] Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe - Copenhagen Economics (2018)

[255] Medicinal & plant protection products – single procedure for the granting of SPCs (europa.eu).

[256] The authorisation of a medicinal product does not mean that it will be immediately accessible to all European patients. Factors such as the size of the population or the organisation of health systems and national procedures influence these decisions. Companies tend to begin negotiations with the Member States that may grant a higher

national decisions on pricing and reimbursement of the medicines concerned, since pricing and reimbursement is the competence of Members States[257].

The **Directive on transparency of measures regulating the prices of medicines** and their inclusion in the scope of national health insurance systems[258] aims at obtaining an overall view of national pricing arrangements, and providing public access to them for all those involved. This Directive regulates the procedural aspects of the Member States' decisions on pricing and reimbursement, e.g. timelines for decisions on pricing and reimbursement, publication of criteria for reimbursement and negative reimbursement decisions have to be justified. It does not impact on the level of price.

To help national authorities in their reimbursement decisions national Health Technology Assessment (HTA) bodies may assess the medicines. The HTA is a scientific evidence-based process to determine the relative effectiveness of new or existing health technologies.

The **Regulation on HTA**[259] establishes a Coordination Group of HTA national or regional authorities, a stakeholder network and lays down rules on the involvement in joint clinical assessments and joint scientific consultations of patients, clinical experts and other relevant experts. The regulation also reduces duplication of efforts for national HTA bodies and industry, facilitates business predictability and ensures the long-term sustainability of EU HTA cooperation. The new rules will come in to force in 2025 and should complement the efforts of the EU general pharmaceutical legislation to incentivise innovation with a strengthened and expanded HTA capacity.

iv. After the market launch stage

Once a medicine is authorised and placed on the market, it is subject to pharmacovigilance. Pharmacovigilance relates to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem. The general EU pharmaceutical legislation details the pharmacovigilance obligations.

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price, often the countries with the highest GDP per capita. The willingness to pay a high(er) price in a Member State with a high GDP may limit the ability of a smaller Member State to negotiate a price in line with its GDP; hence, differences in the accessibility and affordability across the EU.

[257] The decision for pricing and reimbursement is based on national policies, which pertain to Member States and thus are outside the remit of the EU legislation and of this revision.

[258] Council Directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of national health insurance systems, OJ L 40, 11.2.1989, p. 8, EUR-Lex - 31989L0105 - EN - EUR-Lex (europa.eu).

[259] Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU, OJ L 458, 22.12.2021, p. 1, EUR-Lex - 32021R2282 - EN - EUR-Lex (europa.eu).

In addition, the **Regulation on the performance of pharmacovigilance activities**[260] outlines the practical details to be respected by marketing authorisation holders, national competent authorities and the EMA and the **Regulation on post-authorisation efficacy studies**[261] specifies the situations in which such studies may be required.

After an initial authorisation has been granted, market authorisation holders can also develop changes to the medicines. The **Regulation on variations**[262] sets the procedures for post-authorisation changes to a marketing authorisation for medicines. These changes can e.g. be changes in address of the company, active substance, strength, pharmaceutical form or route of administration. The Commission also intends to review this regulation so as simplify the system and reduce administrative burden for medicine authorities and companies.

c. Legislation in adjacent areas

The **legal framework for blood, tissues and cells**[263] (BTC) is used for medical treatments and therapies, including innovative therapies. The ongoing review will promote the safety of patients and donors, facilitate innovation and contribute to adequate supply of the relevant therapies. Blood, tissues and cells may be starting materials for medicines. Particularly important for the pharmaceutical sector is the strengthening the safety and quality requirements of BTC to align with the standards of the pharmaceutical framework for the highest risk preparations. It will also address the (re)emergence of communicable diseases, including lessons learnt from the COVID-19 pandemic, and is thus contributing to the European Health Union.

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[260] Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council, OJ L 159, 20.6.2012, p. 5, EUR-Lex - 32012R0520 - EN - EUR-Lex (europa.eu).

[261] Commission Delegated Regulation (EU) No 357/2014 of 3 February 2014 supplementing Directive 2001/83/EC of the European Parliament and of the Council and Regulation (EC) No 726/2004 of the European Parliament and of the Council as regards situations in which post-authorisation efficacy studies may be required, OJ L 107, 10.4.2014, p. 1–4, EUR-Lex - 32012R0520 - EN - EUR-Lex (europa.eu).

[262] Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products, OJ L 334, 12.12.2008, p. 7, EUR-Lex - 32008R1234 - EN - EUR-Lex (europa.eu).

[263] Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC, OJ L 33, 8.2.2003, p. 30, EUR-Lex - 32002L0098 - EN - EUR-Lex (europa.eu) and Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, OJ L 102, 7.4.2004, p. 48, EUR-Lex - 32004L0023 - EN - EUR-Lex (europa.eu).

The **regulation on medical devices**[264] and **the regulation on in vitro diagnostic medical devices**[265] deal with medical devices, which are products or equipment intended for a medical purpose. In the EU, they must undergo a conformity assessment to demonstrate they meet legal requirements to ensure they are safe and perform as intended. They are assessed at Member State level, but EMA is involved in the assessment sometimes. In some cases, the bodies responsible for the conformity assessment must seek a scientific opinion from EMA before issuing a CE certificate. This is the case essentially when medicines are concerned (e.g. medical devices with an ancillary medicinal substance, companion diagnostics). In some other cases (when the device in ancillary to the medicines), the combined product requires a marketing authorisation.

[264] Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC, OJ L 117, 5.5.2017, p. 1, EUR-Lex - 02017R0745-20200424 - EN - EUR-Lex (europa.eu).

[265] Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU, OJ L 117, 5.5.2017, p. 176, EUR-Lex - 02017R0746-20170505 - EN - EUR-Lex (europa.eu).

ANNEX 8: INTERNATIONAL CONTEXT

Table 42 - **Comparison of criteria for orphan designation in the EU, US and Japan**

	EU	US	Japan
Orphan condition	< 5 in 10,000 in EEA; OR without incentives it is unlikely that the marketing would generate sufficient return to justify the investment.	≤ 6 in 10,000 in US; OR an orphan subset of a non-rare disease; condition where the characteristics of the medicinal product limit its use in a particular subgroup; OR	< 4 in 10,000 in Japan;
Medical need	No satisfactory methods of treatment (or prevention or diagnosis) for life-threatening or chronically debilitating condition exist; OR if any such methods exist the medicinal product must be of significant benefit to those affected by the condition, i.e.: o conferring a clinically relevant advantage; OR o a major contribution to patient care.	Not a criterion unless the same drug has previously been approved for the same use or indication, clinical superiority needs to be proven as follows: Shown to provide a significant therapeutic advantage over an approved drug in one or more of the following ways: (i) Greater effectiveness; (ii) Greater safety in a substantial portion of the target populations; (iii) In unusual cases, where neither greater safety nor greater effectiveness has been shown, a demonstration that the drug otherwise makes a major contribution to patient care.	No appropriate alternative drug/medical device treatment for serious disease including difficult to treat the disease; OR higher efficacy or safety is expected compared with existing products.
Medical plausibility/ scientific rationale	Usually *in vivo* data.	Clinical study data or case reports if available; *in vivo* animal data; *in vitro* data if no clinical or *in vivo* data available	Non-clinical and clinical data in the latter half of the phase I study or in the first half of the phase II study.

TABLE 43 - KEY DIFFERENCES IN THE PROCEDURES FOR ORPHAN DESIGNATION IN THE EU, US AND JAPAN[266]

Items	EU	US	Japan
Application to	Committee for Orphan Medicinal Products (COMP).	Office of Orphan Products Development (OOPD).	Ministry of Health, Labour and Welfare (MHLW)
Timetable	Timetable for submission and assessment published by the Agency.	Any time; no defined timetable;	Any time; no defined timetable;
Key aspects of the application	Prevalence; Medical need; Medical plausibility.	Prevalence. Scientific rationale.	Prevalence; Medical need; Possibility of development.
Sponsor established in territory	Proof of establishment in EU.	Not required.	Not required.
Translations	Translations of product name and proposed orphan indication into all official languages of the EU plus Icelandic and Norwegian.	Not required.	Application in Japanese.

[266] In the US, a medicinal product is eligible for orphan designation when it is intended to treat a disease that affects less than 200 000 persons (which is equivalent to 6 in 10,000) in the US or affects more than 200 000 persons and for which there is no reasonable expectation that the cost of developing and making a medicinal product for such disease or condition will be recovered from sales. In addition, in the US an orphan designation may be given to an orphan subset of a non-rare disease condition where the characteristics of the medicinal product limit its use in a particular subgroup. O'Connor DJ; Expert Opinion on Orphan Drugs (2013), 1(4):255-259.

ANNEX 9: CRITERIA TO IDENTIFY PRODUCTS ADDRESSING UMN AND HUMN

	High UMN **Orphan** medicinal products	UMN **general** pharmaceutical legislation[267]
CRITERIA		
Disease level	Life-threatening or seriously debilitating	Life threatening or seriously debilitating
Product level	[Criteria for designation continue to apply - Article 3 of the Orphan Regulation: <5 in 10 thousand persons in the Community] <u>Case 1</u> • **No medicine is authorised** for the treatment of the disease/condition; **And** • There is **no commonly used (non-pharmacological) method** of treatment whether subject to marketing authorisation or not (e.g. surgery). **And** • The treatment concerns the substantial part of population affected by the orphan disease; **And** • The product does not concern a well-established use product. **[OR]** <u>Case 2</u> • **Treatments exist** but they: - Are symptomatic, not curative; **And** • The treatment under development is a **curative** treatment for the majority of patients affected by the orphan disease.	<u>Case 1</u> • **No medicine is authorised** for the treatment of the disease/condition; **<u>[OR]</u>** <u>Case 2</u> • Medicines are authorised but are not **satisfactory** o Remaining high morbidity or mortality, [or] o Serve less than a certain % of the population affected by the disease, [or] o There is no paediatric indication. **And** <u>In both cases (1 and 2), the new product must:</u> - Have a large treatment effect (reducing morbidity or mortality); [**and**] - Serve a substantial part of population; **[OR]** <u>Case 3</u> - It concerns an **orphan designated medicinal product** that automatically fulfils UMN for general pharma (meaning there is no additional requirement(s))

[267] Criteria applicable also for medicines for children

ANNEX 10: FACTORS INFLUENCING ACCESS TO AFFORDABLE MEDICINES

This annex sets out the different regulatory steps and related decision making processes that have an impact on access and affordability of medicines ("access chain"). Section 1 describes the different steps in the "access chain" from authorisation of medicines to patient access. Section 2 provides further details on pricing and reimbursement policies across the EU and how they can influence access to affordable medicines.

1. **The access chain: from market authorisation of medicines to patient access**

Marketing authorisation is but the first of a number of steps for patients to have access to a medicine. Patient access also requires, following relevant applications by companies, positive HTA assessments and positive pricing and reimbursement decisions by Member States. In addition to those steps, for patients to have access *across the entire EU*, companies have to launch the respective medicine in each Member State. Finally, for a patient to have actual access to a medicinal product, a prescriber has to decide that a medicine is the right treatment choice and prescribe it. The steps from marketing authorisation to patient access can be described along an access chain, which is summarised in the table below. Further details on each step are provided in the following subsections of this section.

Table 44 - Overview *of the access chain: marketing authorisation to patient access*

STEPS	**Scope**	**Legal framework**
1. Marketing authorisation	Quality, safety, efficacy; Positive benefit-risk balance	General pharma framework
2. EU-level Health Technology Assessment (clinical HTA aspects)	Relative clinical effectiveness and relative safety, in comparison to comparator treatment(s) reflecting the standard of care; Supports conclusions on added therapeutic (clinical) value	Regulation (EU) 2021/2282
3. Company decision to launch the medicine in a Member State	Submission of application by the company to national HTA, pricing and reimbursement bodies	

4. National Health Technology Assessment	Takes into account the EU-level assessment of clinical HTA aspects; Focuses on context-specific, non-clinical HTA aspects (e.g. economic, organisational); Supports conclusions on cost-effectiveness, budget impact, value for money	National/regional legislation
5. National pricing and reimbursement	Decisions on reimbursement and pricing; Takes into account added therapeutic (clinical) value, economic considerations (cost-effectiveness, budget impact, affordability), healthcare system and societal context	National/regional legislation Directive 89/105/EEC (covering only timeline, process)
6. Prescription	Evidence-based medicine, taking into account clinical guidelines and medical protocols and the individual patient situation	

1.1 Marketing authorisation

For the marketing authorisation of a medicine, the regulator will consider the quality, safety and efficacy of the medicine and authorise it if the medicine has a positive benefit-risk balance for the patient. Accordingly, data requirements for marketing authorisation reflect the need to show quality, safety and efficacy of a particular medicine. "Downstream" steps in the access chain (health technology assessment, pricing and reimbursement) often require additional data to show an added value of a newly authorised medicine compared to already existing medicines/treatments (see sections 1.2, 1.4 and 1.5).

It should however be noted though that even medicines which appear similar at the time of launch may over time prove to have different efficacy or safety profiles in particular subgroups of patients. Furthermore, the effect of treatment in individual patients may differ from the population-level effects seen in clinical trials. With greater choice, patients will have a better chance of finding a treatment most appropriate to their needs. For these reasons, EU regulations on marketing authorisation do not require that new medicines be superior to medicines already on the market.

1.2 EU-level Health Technology Assessment (clinical HTA aspects)

Health technology assessment (HTA) evaluates the added value of a new medicine in comparison to existing medicines (or other treatments) that reflect the current standard of care. HTA is an evidence-based approach that helps Member States to provide the optimal health care outcome for patients with limited budgets. Accordingly, HTA is used by Member States across the EU in particular for innovative and costly medicines, as a tool to support pricing and reimbursement decisions. However, there is considerable diversity across Member State HTA systems in terms of procedural frameworks, methodological approaches, and available resources and expertise.

In 2022, Regulation (EU) 2021/2282 on health technology assessment entered into force. It provides a legal framework for strengthened EU cooperation on HTA, focusing on clinical aspects of HTA (including the development of common methodologies). From 2025 onwards, Member State HTA bodies will jointly assess *clinical* HTA aspects (comparative clinical effectiveness and safety) of centrally authorised innovative medicines (Joint Clinical Assessment).[268] Such Joint Clinical Assessments will have to be taken into account by Member States in their national HTA processes. Joint Clinical Assessments will be high quality, timely scientific reports (available within 30 days from marketing authorisation). They will enable Member States to focus their limited national HTA resources on assessing more context-specific, non-clinical aspects of HTA (see section 1.4).

Clinical data generated for marketing authorisation purposes (to demonstrate safety and efficacy of the individual product) are not always considered sufficient for HTA and down-stream pricing and reimbursement purposes, which rely on demonstration of comparative effectiveness and safety (i.e. added therapeutic value over existing medicines/treatments).[269,270,271] HTA bodies generally require clinical trials that include an active comparator arm (rather than a placebo-controlled trial or a single-arm trial). HTA bodies also often see challenges with clinical trial data that are less mature and come with higher uncertainties, e.g. in the context of conditional marketing authorisations.[272] When HTA bodies consider the available clinical data inappropriate or insufficient for demonstrating an added therapeutic value, this can lead to delays and

[268] Step-wise implementation of the product scope: oncology and advanced therapy medicines from 2025, orphan medicines from 2028, all centrally authorised innovative medicines (new active substances) from 2030.

[269] Evidence gaps for drugs and medical devices at market entry in Europe and potential solutions - KCE (fgov.be).

[270] Bloem LT, Mantel-Teeuwisse AK, Leufkens HGM, De Bruin ML, Klungel OH, Hoekman J. Postauthorization Changes to Specific Obligations of Conditionally Authorized Medicines in the European Union: A Retrospective Cohort Study. Clin Pharmacol Ther. 2019;105(2):426-35.

[271] Banzi R, Gerardi C, Bertele V, Garattini S. Conditional approval of medicines by the EMA. BMJ. 2017;357:j2062.

[272] In the interest of public health, a conditional marketing authorisation may be granted for such medicines on less comprehensive clinical data than normally required subject to legally binding obligations for the marketing authorisation holder to generate the comprehensive data after the authorisation.

negative results in the downstream decision-making process on pricing and reimbursement.[273, 270, 271]

From a company perspective, the conduct of clinical trials that generate the comparative evidence required for HTA purposes can be more risky, more costly or take longer. Companies have also faced challenges related to lack of clarity on data needs for HTA, given the diversity of HTA systems and methodological frameworks across Member States. Companies have therefore traditionally (first) focused on the data needs for marketing authorisation when designing their clinical trials. This is however changing and there have been increasing calls by pharmaceutical companies and other stakeholders for more early dialogues on evidence needs along the lifecycle of products and for scientific advice on evidence generation.[270, 271]

For this reason, the new HTA Regulation (Regulation (EU) 2021/2282) provides also a legal framework for scientific advice by HTA bodies to companies on clinical trial design (common HTA advice, agreed at the level of the Member State Coordination Group on HTA), in parallel with scientific advice by the European Medicines Agency provided for marketing authorisation purposes. While respecting the different remits of marketing authorisation and HTA, this parallel scientific advice aims to ensure the generation of evidence that meets the requirements of both frameworks. Parallel scientific advice has already been successfully piloted in the context of EU-funded projects (in particular the Joint Actions EUnetHTA in cooperation with EMA).[274]

1.3 Company decision to launch the medicine in a Member State

It should be noted that while a marketing authorisation at EU level allows for a medicine to be placed on the market in all Member States, the actual market launch in a given Member State is exclusively the decision of the marketing authorisation holder. Company decisions are commercial decisions that take into account whether there is a 'market' for the medicine in a given Member State from a business point of view, considering factors such as market size, price levels, promotion and distribution networks, regulatory requirements, current or future patient population, medical protocols and national pricing and reimbursement policies such as external reference pricing (see Section 2 on pricing and reimbursement policies for further details). Factors related to the healthcare system can also influence the decision, e.g. the availability of specialised equipment or infrastructure to deliver the medicine (in particular in the case of advanced therapy medicines), or national treatment preferences. If the conditions for a positive business case are met, the company will initiate the procedures required for

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[273] Vreman RA, Bouvy JC, Bloem LT, Hövels AM, Mantel-Teeuwisse AK, Leufkens HGM, Goettsch WG. Weighing of Evidence by Health Technology Assessment Bodies: Retrospective Study of Reimbursement Recommendations for Conditionally Approved Drugs. Clin Pharmacol Ther. 2019 Mar;105(3):684-691. doi: 10.1002/cpt.1251. Epub 2018 Nov 8. PMID: 30300938; PMCID: PMC6587700.

[274] Parallel joint scientific consultation with regulators and health technology assessment bodies | European Medicines Agency (europa.eu)

market launch in that Member State (by submitting applications for HTA, pricing and reimbursement, in accordance with national legal/procedural frameworks).

Smaller and less wealthy countries will often see fewer product entries (due to smaller market potentials). For these countries, the time to availability is also significantly longer. The average time to market from marketing authorisation in Europe differs greatly: for example, for cancer drugs, in the period 2011-2018, it ranged from 17 to 1.187 days, with the shortest delays in Germany, the UK and Austria (less than 31 days) and the longest delays in Greece and Estonia (more than 950 days).[275] In other cases, medicines became available in Central and Eastern Europe only several years after marketing authorisation[276], with market launch delayed up to three years on average in Central-Eastern Europe.[277] It should however be noted that a lack of access to a specific medicine does not necessarily imply lack of access to effective treatment, if appropriate therapeutic alternatives are accessible.[278]

1.4 National Health Technology Assessment

For medicines for which HTA is conducted to support pricing and reimbursement decisions (usually for innovative, costly medicines), the national HTA procedure is usually triggered by marketing authorisation holders launching a pricing and reimbursement application in the Member State concerned.

Currently, HTA bodies assess both clinical aspects (comparative effectiveness and safety) and non-clinical aspects (e.g. economic, organisational, social, ethical) at national level. From 2025 onwards, assessments of clinical HTA aspects will be conducted jointly at EU level (Regulation (EU) 2021/2282), and HTA work at national level is expected to focus on non-clinical HTA aspects (see section 1.2). Clinical HTA analyses support pricing and reimbursement authorities in drawing conclusions on added therapeutic value, while economic HTA analyses support them in concluding on cost-effectiveness, value for money and budget impact.

1.5 National pricing and reimbursement decision

Pricing and reimbursement rules and policies are an exclusive competence of Member States (Article 168 TFEU). Due to historical, political, legal and economic developments, a large variety in pricing and reimbursement regulations have developed across Member States. Moreover, the overall organisation and funding of national healthcare systems differ significantly.279

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[275] Uyl-de Groot, C., Heine, R., Krol, M., and Verweij, J. 'Unequal Access to Newly Registered Cancer Drugs Leads to Potential Loss of Life-Years in Europe, Cancers, 2020.

[276] Vogler, S., Schneider, P., and Zimmermann, N., 'Evolution of Average European Medicine Prices: Implications for the Methodology of External Price Referencing', PharmacoEconomics, 303-309, 2019.

[277] Maini, L., & Pammolli, F., Reference Pricing as a Deterrent to Entry: Evidence from the European Pharmaceutical Market, 2017.

[278] OECD (2018), Pharmaceutical Innovation and Access to Medicines, OECD Health Policy Studies, OECD Publishing, Paris, https://doi.org/10.1787/9789264307391-en.

[279] Health System in Transition Reviews (HiT) (who.int)

National and/or regional pricing and reimbursement policies assess the size of the patient population and budget impacts, and negotiate the price. Often, late market entries in some Member States are driven by a combination of business decisions and national pricing/reimbursement policies, such as external reference pricing, leading marketing authorisation holders to market their medicines first in Member States where a high price can be obtained (see section 2 on pricing and reimbursement policies across the EU for further details). Some Member States, e.g. Greece, require proof of a positive reimbursement decision in comparable countries before an HTA assessment can be initiated.280

Pharmaceutical expenditure is largely subsidised by national health systems in order to ensure the adequate provision of medicines to all citizens. In this context, Member States adopt measures to regulate the prices of medicines and the conditions of their public funding. Such measures influence the prescription and utilisation of medicines in each Member State and also affect the decisions of and possibilities for pharmaceutical companies to sell their products in national markets. Industry stakeholders claim delays in national pricing and reimbursement decisions that would contribute to postponing the market entry of medicines after the granting of a (central) marketing authorisation. However, a factor that can contribute to delays in national pricing and reimbursement decisions is a lack of appropriate evidence on the added therapeutic value of the product, or evidence that suggests only a minor added therapeutic value (see sections 1.2, 1.4 and 2.2).

Directive 89/105/EEC ('Transparency Directive') is the only EU legal instrument in relation to the applicable national rules on pricing and reimbursement of medicines. The Directive is built on the principle of minimum interference in the organisation of national social security systems. It lays down a series of procedural requirements to ensure the transparency of national decisions on pricing and reimbursement, such as a timeline of 180 days (with the possibility of extension or suspension of the timelines), and procedures such as requirements for publishing the outcomes of national decisions. In light of the Treaty rules on free movement of goods (Article 34 TFEU), the Directive has the objective to avoid barriers to trade created by national measures.[281]

It should be noted that the Transparency Directive refers to the transparency of the pricing and reimbursement process, but not the transparency of prices. In general, prices are publicly available only in form of 'list prices'. These list prices are increasingly disconnected from the actual prices paid. Typically and in particular for products with high price and high uncertainty, confidential price discounts[282] or managed entry

[280] Kourlaba, Georgia & Beletsi, Alexandra. (2021). Time to Patients' Access to New Medicines in Greece: Evaluation of Health Technology Assessment (HTA) Process from July 2018 until January 2021.

[281] An update of the Directive had been proposed by the European Commission in 2012, however it was officially withdrawn in 2015. A dedicated study will be launched in 2023 to take stock of the implementation challenges and to explore how Directive 89/105/EEC could further contribute to the affordability objectives of the Pharmaceutical Strategy.

[282] There is little public data on confidential prices; however there are indications that it may be broadly on average around 20% of the pharmaceutical budget, with high variation across products and countries. Steven G. Morgan, Sabine Vogler, Anita K. Wagner, Payers' experiences with confidential pharmaceutical

agreements are in place (see section 2 on pricing and reimbursement policies). In a 2022 working paper, the OECD summarised the complex impacts of the **lack of price transparency**: "*It can be argued that confidentiality assists payers in achieving more favourable net prices, and companies in price discriminating between countries, which promotes equitable access [...]. At the same time, however, confidentiality is undermining the confidence of both payers and patients about the industry, and further challenging policy makers in attempting to find a balance between rewarding innovation, delivering affordable access, and maintaining the sustainability of health systems.*"[283]

1.6 Prescription and use

For a patient to have access to prescription medicines, a prescriber will first have to consider whether this medicine is the appropriate choice for the patient. Then, the patient will need to accept and adhere to the proposed treatment. Prescribers make an informed choice based on clinical guidelines or treatment protocols that provide information on the added clinical benefit of the available treatment options and support the identification of a first line choice. Clinical guidelines sometimes take into consideration the affordability to health systems and patients. Inclusion of a medicine in clinical guidelines and treatment protocols is an important factor influencing a company's decision to launch a medicine in a given market. The prescription of medicines can also be influenced by industry promotion and detailing. A company will seek to gain prescriptions by actively differentiating its product from alternative treatments, through promotion activities vis-à-vis doctors, training of nurses, patient support programmes, etc.

1.7 *Alternative access chains*

The health impact of late market entries is mitigated by the fact that innovative therapies are often accessible for patients through exceptions, such as compassionate use/named patient use schemes. Some countries have established "(innovation) funds" for defined medicines which are expensive but still considered important for patients, so they are financed out of funds that bypass the "standard" reimbursement processes. Furthermore, a medicine may be brought to a national market outside the national reimbursement scheme and will need to be paid for by private insurance or out-of-pocket payments. Depending on the national health systems, medicines may enter the market without national pricing or reimbursement decisions. This would be the case for many non-prescription medicines. However, in the absence of a reimbursement decision, the patient has to pay to out-of-pocket.

2. Pricing and reimbursement policies across the EU

Member States have developed a large variety of pricing and reimbursement institutional frameworks and policies, some of which are explained in further detail below.[284] While there are overviews and comparisons of the different systems, the impact of the different organisational systems on access and affordability is complex and has not yet been modelled in a comprehensive way.

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price discounts: A survey of public and statutory health systems in North America, Europe, and Australasia, Health Policy, Volume 121, Issue 4, 2017, Pages 354-362, ISSN 0168-8510.

[283] OECD Health Working paper 146. Exploring the consequences of greater price transparency on the dynamics of pharmaceutical markets. 2022. c9250e17-en.pdf (oecd-ilibrary.org)

[284] Medicines Reimbursement Policies In Europe. WHO Europe. 2018

Regarding the institutional framework, a wide variety of different organisations and structures have been set up in the various EU Member States. The organisations responsible for marketing authorisation, health technology assessment and pricing and reimbursement may be part of the same organisation (e.g. Portugal, Cyprus, Czechia), organised decentrally (e.g. Denmark, Spain, Italy), combining regulatory and HTA functions (Finland, Hungary) or combining pricing and/or reimbursement and HTA functions (Latvia, Luxembourg, Malta, Netherlands).[285]

2.1 External reference pricing

The large majority of Member States apply, amongst others, external reference pricing (ERP), which considers a basket of prices of the same medicine in other countries (e.g., the average, or the average of a certain number of the lowest prices, or the lowest price) as a basis for pricing – and sometimes also reimbursement – decisions[286]. Considering that ERP strongly influences national prices, it has a direct impact on any companies' business case for launching medicines in different national markets. Accordingly, ERP influences also the path of launch of medicines across Europe.

Sequencing of market entry in the EU – typical patterns of pharmaceutical companies

Marketing authorisation holders choose the sequence of market entry to maximise their gains and limit the spill-over of lower prices in a given Member State on another Member State. There are fixed costs associated with entering a national market (e.g., procedural, or related to the packaging). Pharmaceutical companies primarily focus on Member States with significant market potential, taking into account the population size and the public pharmaceutical budget per capita. Companies set their prices based on the market conditions in Member States with greater market potential and purchasing power, not necessarily considering the affordability for lower income countries.[287] Overall, pharmaceutical companies tend to launch their medicines (first) in northern and western Member States with high purchasing power. The sequence of launch typically starts in Germany, where there is free pricing in the first year[288], followed by other large markets with high purchasing power, such as Italy, France, Spain, or smaller markets with high price levels, such as Denmark, Sweden or Luxemburg. To limit the spill-over effects resulting from the ERP system, the marketing authorisation holders

[285] Mapping of HTA national organisations, programmes and processes in EU and Norway (Study by European Commission)
[286] Euripid Guidance Document on External Reference Pricing (ERP)
[287] Access to high-priced medicines in lower-income countries in the WHO European Region
[288] Once a medicine receives marketing authorisation, it can be launched on the German market at a price determined by the pharmaceutical company. An HTA is conducted during the first year as a basis for negotiations on the price that will be reimbursed from the thirteenth month. If the negotiated reimbursement price is below the price charged during the first year, no payback is required from the company. Payer Policies To Support Innovation and Access To Medicines in the Who European Region – WHO OMI technical report - https://www.who.int/europe/publications/i/item/9789289058247

and public authorities have to agree on confidential prices, while maintaining higher list prices. ERP applies to list prices, and is detrimental to transparency of prices. While ERP may improve affordability, it can have an impact on accessibility. For instance, the Slovak Ministry of Health allowed for a 10% higher launch price than reference pricing countries so that pharmaceutical companies would not delay launching. Evidence shows that manufacturers often delay market access to Belgium to avoid creating a Belgian reference price – as it is typically not among the highest in the EU.[289]

2.2 Value based pricing

Another common method is the **value based pricing**, which implies that prices are formed by reference to a medicine's value (value for money). Value is most often measured by cost per QALY (quality adjusted life years). Some medicines may have a low cost per QALY and would be considered good value for money. Medicines with a high cost per QALY would not be considered good value for money. To give an idea of the range of values, prevention and vaccination have typically a low cost per QALY (from 500-5000 EUR e.g. HPV vaccination, maternal vaccination for pertussis), whereas certain interventions have systematically higher QALYs (e.g. end-of life oncology treatments, rare diseases can be over 100 000 EUR/QALY).[290, 291] In these cases, there is a political and ethical choice to be made (whether a QALY is a QALY, no matter to whom it accrues). However, QALYs are easier to interpret when comparing interventions to the same person – to prioritise treatments that bring more benefits (at a lower cost/QALY) to the same patient. Explicit thresholds are in place in e.g. Poland, Hungary, Slovakia and Ireland[292] – around the range of 30 000 - 50 000 EUR/QALY. A debate about pros and cons is recurrent[293] – a major downside is that regardless of the R&D and production costs, the value-based price would tend to be set at the relevant threshold.[294]

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[289] Fontrier, AM., Gill, J. & Kanavos, P. International impact of external reference pricing: should national policy-makers care?. Eur J Health Econ 20, 1147–1164 (2019).

[290] Kocot, E., Kotarba, P. & Dubas-Jakóbczyk, K. The application of the QALY measure in the assessment of the effects of health interventions on an older population: a systematic scoping review. *Arch Public Health* 79, 201 (2021). https://doi.org/10.1186/s13690-021-00729-7

[291] Postma, M.J., Noone, D., Rozenbaum, M.H. *et al.* Assessing the value of orphan drugs using conventional cost-effectiveness analysis: Is it fit for purpose?. *Orphanet J Rare Dis* 17, 157 (2022). https://doi.org/10.1186/s13023-022-02283-z

[292] Rogalewicz, Vladimir & Barták, Miroslav. (2017). QALYs and cost-effectiveness thresholds: critical reflections.

[293] Bertram, M. Y., Lauer, J. A., De Joncheere, K., Edejer, T., Hutubessy, R., Kieny, M. P., & Hill, S. R. (2016). Cost-effectiveness thresholds: pros and cons. *Bulletin of the World Health Organization*, *94*(12), 925–930. https://doi.org/10.2471/BLT.15.164418

[294] Such process can be observed in oncology medicines, Howard et al. (2015) document price increases in the anticancer medicines market of about 10% a year in the past 20 years, after controlling for increased benefits (survival). Cost changes are deemed unlikely to be behind the price increases. David H. Howard & Peter B. Bach & Ernst R. Berndt & Rena M. Conti, 2015. "Pricing in the Market for Anticancer Drugs," Journal of Economic Perspectives, vol 29(1), pages 139-162.

While innovative medicines receive marketing authorisation on the basis of an evaluation of their quality, efficacy and safety and a positive benefit-risk balance, as explained, downstream actors (HTA bodies and pricing and reimbursement authorities) require evidence on therapeutic added value (see section 1 on the access chain). Several studies across multiple indications and countries (e.g. Germany[295], France, or Italy[296]) suggest that a significant percentage of innovative medicines come to the market with insufficient evidence on added therapeutic value or evidence that suggests only a minor added therapeutic value, while industry sets prices for these medicines nevertheless at high level to cover R&D, production and other costs.[297,298] In such situations, it becomes difficult for payers to justify spending large amounts of their budgets on medicines that cannot show proven and significant added therapeutic value.

It should however be noted that for marketing authorisation purposes, a new medicine is and should not be required to be superior to medicines already authorised. This is because the effect of treatment in individual patients may differ and with greater choice of treatment, patients will have a better chance of finding a treatment most appropriate to their needs (see section 1 on the access chain). In other words, even if medicines are not superior to other medicines based on a direct, average comparison, those medicines can still offer important second or third line treatment options for individual patients.

2.3 Costplus-pricing

With costplus-pricing, the price of medicines is set by assessing production costs (incl. R&D costs, manufacturing, regulatory processes and compliance, overheads, operational costs) and adding a profit margin.[299] Although, in theory, this pricing policy is straightforward with clear and justifiable pricing rules that provide a level of certainty for budgetary planning and profits for the suppliers, it is not widely used for setting medicines prices at the ex-manufacturer or ex-wholesaler level. This may be partially due to the fact that it is currently difficult to implement because obtaining reliable cost information from suppliers is difficult.[300] Another, more fundamental reason may be that in a market economy, which is considered a crucial driver for investment and innovation, particularly valuable innovations yield higher returns than less valuable ones, rewarding the risk-taking investor for success in creating value.

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[295] Wieseler, B. et al. (2019) New drugs: where did we go wrong and what can we do better? BMJ 2019;366:l4340 doi: 10.1136/bmj.l4340

[296] Analysis on added therapeutic value of innovative pharmaceuticals by national authorities find similar results (cf. HAS statistics in France, or GRADe classification in Italy).

[297] Improving Access To Innovative Medicines Opinion by the Expert Panel on Effective Ways of Investing in Health (EXPH) factsheet_innovative_medicines_en_0.pdf (europa.eu)

[298] Revue Prescrire N° 448, p. 142-143

[299] AIMs-fair-pricing-model-Accompanying-paper-to-the-fair-pricing-calculator_June2021.pdf (aim-mutual.org)

[300] World Health Organization. (2021). Cost-plus pricing for setting the price of pharmaceutical products: WHO guideline on country pharmaceutical pricing policies: a plain language summary. World Health Organization. https://apps.who.int/iris/handle/10665/341902. License: CC BY-NC-SA 3.0 IGO

There is a lack of transparency on research and development costs, often triggering criticism by policymakers and stakeholders.[301] The pharmaceutical industry estimates the research and development (R&D) costs for developing a medicine between US$2.2 billion and 2.9 billion. However, this figure is heavily contested by others. Irrespective, industry uses these figures to rationalise and justify the high prices charged for certain medicines.[302] Although companies' annual reports provide certain insights on overall R&D spending, companies do not do not disclose the relevant R&D costs spent on individual medicines brought onto the market. Either way, the market risks associated with R&D costs need to be put in perspective with the generated revenues.

Another point of concern is that the contribution of public funding to R&D costs is not known. By way of example, there is no clarity on the amounts of public funding spent on biomedical R&D in European countries. While the pharmaceutical industry claims that it has been paying for all costly clinical trials, this was contradicted by a study[303] financed by the Dutch government.

2.4 Managed entry agreements

A managed entry agreement (MEA) is a contractual arrangement between a manufacturer and health care payer/provider that enables access to (or reimbursement of) a novel medicinal product, subject to conditions. The objective of a MEA is twofold: to allow access to new high-priced medicines that would otherwise not be affordable, and to manage the uncertainty of limited evidence on clinical outcomes.[304] There are two basic categories of MEAs: finance-based (such as price–volume agreements) or performance-based (based on health outcomes).[305] Confidentiality is a major feature of all types of MEA. In some Member States, it is not even known which medicines are subject to an MEA, or which types of MEA are in use.[306] Experts agree that MEA are becoming more prevalent and could result in increasingly non-transparent prices "involving a mix of rebates across groups of medicines, discounts by indication, or based on volumes or expenditure caps, all of which mean it is complex to compute the final transaction price of a product."[307]

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[301] https://www.who.int/europe/publications/i/item/9789289058193

[302] Schipper, Irene & de Haan, Esther & Cowan, Roberta. (2019). Overpriced Drugs Developed with Dutch Public Funding.

[303] Schipper, Irene & de Haan, Esther & Cowan, Roberta. (2019). Overpriced Drugs Developed with Dutch Public Funding.

[304] Vogler S (2022): Payer policies to support innovation and access to medicines in the WHO European Region. Copenhagen: World Health Organization, Regional Office for Europe

[305]Medicines Reimbursement Policies in Europe. 2018. https://apps.who.int/iris/bitstream/handle/10665/342220/9789289053365-eng.pdf?sequence=1&isAllowed=y

[306] Pauwels K, Huys I, Vogler S, Casteels M, Simoens S. Managed entry agreements for oncology drugs: lessons from the European experience to inform the future. Front Pharmacol. 2017;8:171. doi:10.3389/fphar.2017.00171

[307] OECD Health Working paper 146. Exploring the consequences of greater price transparency on the dynamics of pharmaceutical markets. 2022. c9250e17-en.pdf (oecd-ilibrary.org)

2.5 Policies for generic and biosimilar competition

Member States have implemented a variety of pricing and reimbursement policy measures for off-patent medicines (including generic and biosimilar medicines) to promote competition, increase spending efficiency and contribute to access to innovation at affordable prices on patent expiry, and free up funds to be used for innovation.[308] Those include – but are not limited to – incentives for prescribing biosimilars and policies related to INN prescribing, switching by physicians and substitution by pharmacists. Acceptance and trust of biosimilar medicines by patients and health professionals is of utmost importance to enhance biosimilar uptake. There have been concerns by health professionals and patients as regards comparability of the biosimilar and originator, even though the available switching data does not indicate that switching from a reference product to a biosimilar is associated with any major efficacy, safety, or immunogenicity issues.[309,310] Recently, EMA and HMA published a joint statement to confirm the interchangeability of biosimilars to address this issue.[311]

Biosimilar competition

'Older' products (i.e. with expired protection period) are an important factor of pharmaceutical spending. Competition – generic and biosimilar – improves access and drives down prices. Due to the typically high prices charged for biological medicines, creating competition for their markets through the introduction of biosimilar versions can generate substantial cost savings[312]. In Germany, the waiting time for patients with rheumatoid arthritis to be treated with a biologic has been reduced from 7.4 years to 0.3 years after the introduction of biosimilars.[313] Looking at list price changes in markets with biosimilar competition, by 2020, biosimilars reduced the cost by almost 1/3.[314] One study estimated the impact of biosimilar entry in terms of healthcare systems savings between 2007 and 2020 for eight EU countries (France, Germany, Italy, Poland, Romania, Spain, Sweden, and the UK), ranging from €11.8 billion to €33.4 billion.[315]

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[308] Vogler S (2022): Payer policies to support innovation and access to medicines in the WHO European Region. Copenhagen: World Health Organization, Regional Office for Europe

[309] Mestre-Ferrandiz, J., Towse, A. & Berdud, M. Biosimilars: How Can Payers Get Long-Term Savings?. *PharmacoEconomics* **34,** 609–616 (2016).

[310] Barbier L, Ebbers HC, Declerck P, Simoens S, Vulto AG, Huys I. The Efficacy, Safety, and Immunogenicity of Switching Between Reference Biopharmaceuticals and Biosimilars: A Systematic Review. Clin Pharmacol Ther. 2020 Oct;108(4):734-755. doi: 10.1002/cpt.1836. Epub 2020 Apr 30. PMID: 32236956; PMCID: PMC7540323.

[311] https://www.ema.europa.eu/en/documents/public-statement/statement-scientific-rationale-supporting-interchangeability-biosimilar-medicines-eu_en.pdf

[312] Farfan-Portet M-I, Gerkens S, Lepage-Nefkens I, Vinck I, Hulstaert F. Are biosimilars the next tool to guarantee cost-containment for pharmaceutical expenditures? The European Journal of Health Economics. 2014;15: 223-8.

[313] https://www.pharmatimes.com/magazine/2021/may_2021/15_years_of_biosimilar_access_in_europe

[314] IQVIA. The Impact of Biosimilar Competition in Europe. 2020. Available from: https://health.ec.europa.eu/system/files/2021-01/biosimilar_competition_en_0.pdf

[315] Haustein R, De Millas C, H er A, et al. Saving money in the European healthcare systems with biosimilars. Gabi Journal. 2012;1(3–4):120–126.

The importance of biosimilar competition has been growing since the first products entered the market in 2006. In 2020, biosimilar medicines accounted for 9% of the sales value of biological medicines in Europe. Nonetheless, uptake of biosimilars varies greatly across Europe. The share of sales of biosimilar medicines among all pharmaceutical sales in hospitals ranges from less than 2% in Bulgaria to 16.5% in Norway (the latter invested heavily in generating and disseminating evidence about safety of switching patients to biosimilar medicines). This variation may be partly explained by the range of different policies to encourage biosimilar uptake.[316]

2.6 Cross-country cooperation activities: regional joint negotiations or joint procurement

Several national governments have established cross-country collaboration initiatives on pricing, reimbursement and/or procurement to address the challenges to ensure access to high-priced medicines. The BeNeLuxA Initiative has concluded successful joint negotiations and further collaborates on horizon scanning, HTA, price and reimbursement negotiations and information sharing. The Nordic Pharmaceutical Forum and the Baltic Procurement Initiative have successfully concluded several joint tender processes for medicines and vaccines. Joint procurement is seen by some as a promising tool to help make small markets more attractive for suppliers, and therefore contributing to availability of medicines that would otherwise not be supplied.

2.7 Related EU cooperation activities

The decisions on the pricing and reimbursement of medicines are an exclusive competence of Member States (Article 168 TFEU). However, the Pharmaceutical Strategy points out that EU and national rules that do not directly regulate prices or reimbursement levels may also have a bearing on the affordability of medicines. In the implementation of the Strategy, the Commission has relaunched the cooperation between National Competent Authorities for Pricing and Reimbursement and the Healthcare Payers (NCAPR group). Through this group, the Commission supports mutual learning and best-practice exchange, including on pricing, payment and procurement policies. This work is based on voluntary and non-legislative actions.

ANNEX 11: SME

Micro and small businesses are an important sub-group driving innovation in medicines,317 particularly in sectors that are under-served due to technological challenges or lower expected market potential, such rare diseases.

The Agency has more than 1,900 EU-based SMEs registered in its corporate database (end 2020), and the European Confederation of Pharmaceutical Entrepreneurs

[316] Draft final report on the Study on Best Practices in the Public Procurement of Medicines (2022), not published.
[317] https://www.labiotech.eu/best-biotech/european-biotech-companies/.

(EUCOPE), which is Europe's principal trade body for small and mid-sized innovative companies working in the field of pharmaceuticals and medical technologies, has around 2,600 SME members

SMEs – and start-ups in particular – represent an important stepping-stone in the overall drug development space, providing a route for public science to push through discovery and pre-clinical research, moving through subsequent development phases and on to regulatory approval. SMEs have greater flexibility and lower costs and have an ability to signal potential to venture capitalists and launch IPOs in a way that is less easy for larger firms.

Pharmaceutical and biotechnology SMEs face additional market barriers as compared with their larger counterparts. The challenges are particularly significant given the very large cost, lengthy timelines and regulatory hurdles associated with the development of new medicines (e.g. 10 years from pre-clinical research through to regulatory approval with high attrition rates at each stage).

The EMA's engagement with SMEs has increased steadily since its set up its SME office in 2005 to provide advice and guidance, organise topical workshops and produces a dedicated newsletter for SMEs registered with EMA. The SMEs also have access to various fee incentives to support their medicine development programmes. The EMA annual report 2020 provides a series of data giving a sense of the scale – and trend – in SME engagement: the SME office received 222 requests for direct assistance on administrative or regulatory aspects and organised 10 briefing meetings to assist SMEs that were unfamiliar with the EU regulatory system. SMEs submitted 23 marketing authorisation applications, which is 19% of all applications received in 2020. Out of the 23 applications, 13 were for orphan-designated medicines. The CHMP gave a positive opinion for 16 medicines developed by SMEs. This is the highest number in the past five years and represents 18% of all positive opinions in 2020. Half of the medicines developed by SMEs (8) contained a new active substance.

Consultation of SME stakeholders

Given the nature of the SME community – large, diffuse with relatively limited time and capacity to engage with public policy – their direct participation in the consultation activities was limited. However SMEs were represented by the views of the European Confederation of Pharmaceutical Entrepreneurs (EUCOPE), which is Europe's principal trade body for small and mid-sized innovative companies working in the field of pharmaceuticals and medical technologies.

Impact.

When possible the impact on SMEs has been identified and described in the relevant sections of the document.

ANNEX 12 COHERENCE WITH THE REVISION OF THE GENERAL PHARMACEUTICAL LEGISLATION

The general EU pharmaceutical legislation regulates the way medicines (including medicines for rare diseases and children) are *authorised* across the EU and sets the framework in which they are marketed.

The Regulation on medicines for rare diseases is an 'add-on' to the general pharmaceutical legislation setting specific measures needed to address the market failure for medicines for rare diseases due to their small populations and potentially limited return on investment. The drivers for unmet medical need in the area of rare diseases remain relevant and therefore requires measures complementary to those provided by in the general pharmaceutical legislation.

Specialised legislation for rare diseases and children, entered into force in 2000 and 2007 respectively and currently being revised, complements the general EU pharmaceutical legislation to specifically support the development in these previously neglected areas, mainly through additional incentives and obligations.

The revision of the general pharmaceutical legislation and of the Regulations on medicines for rare diseases and for children are part of the same intervention aiming at achieving the same objectives set by the Pharmaceutical Strategy, including addressing unmet medical need of patients and access to medicines.

Unmet medical need / *high* unmet medical need

Both revisions will include a criteria-based definition on unmet medical need. The general pharmaceutical legislation will contain a definition for 'unmet medical needs' (UMN). The legislation on rare diseases will contain a definition of '*high* unmet medical needs' (HUMN), as in principle all orphan medicines will automatically satisfy the definition of UMN under the general rules; only a small subgroup of orphan medicines will qualify as 'HUMN'. The Commission has worked with Member States and the EMA and received input from stakeholders via consultations to develop criteria that can be introduced in the legislation. These criteria relate to disease level (whether the disease is life-threatening and/or seriously debilitating) and they relate to product level (whether there is another medicine or therapy already authorised and, if so, whether the treatment under development can satisfactorily cure the disease).

In principle, medicines that satisfy the definition of UMN or HUMN will receive (a) access to early scientific advice and regulatory facilities and (b) access to longer regulatory protection periods (market exclusivity for medicines for rare diseases and data protection for other medicines).

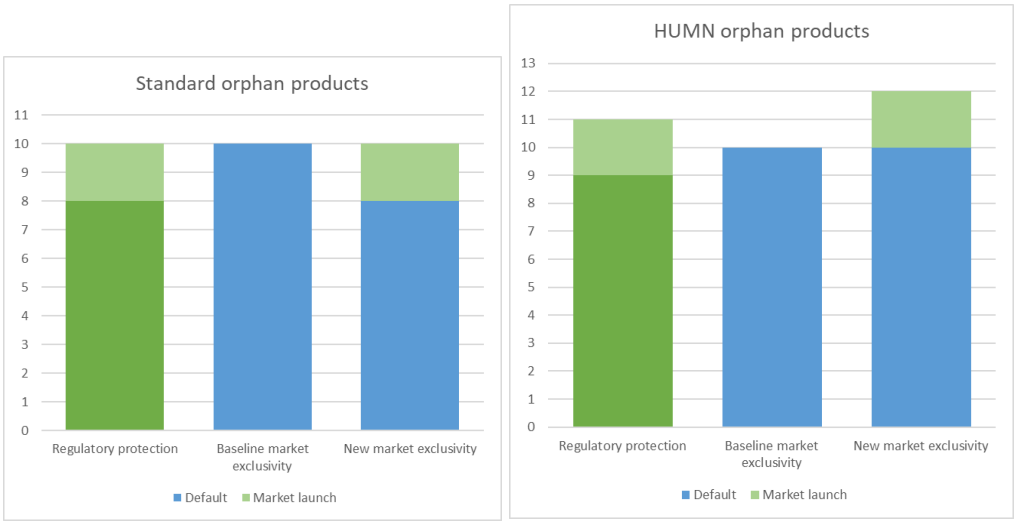
Both the revision of the general pharmaceutical legislation and the revision of the legislation for medicines for rare diseases and children adjust the system of incentives and depart from the 'one size fits all' approach to a 'modulated' one. Therefore, regulatory data protection for medicines and market exclusivity (in the case of orphan medicines) are modulated to reward companies developing medicines that deliver on needs of patients. Such needs are primarily reflected in the concepts of 'unmet medical need'.

The interplay between the regulatory protection and the orphan market exclusivity

(special protection for medicines for rare diseases) will be explained in detail in the revised impact assessment for the Regulations on medicines for rare diseases and for children. Essentially, the market exclusivity will be modulated in the same way as the regulatory protection, 2 or 1 years of the protection will be conditional to all EU market launch (depending which variation of the regulatory protection will be chosen by the legislator). For standard orphan medicines the market exclusivity will be equal to the regulatory protection (as today) and for medicines addressing high unmet medical needs, the market exclusivity will be one year more than the regulatory protection (these medicines will already enjoy a 1-year longer regulatory protection). Please note that the market exclusivity does not only protect from generic competition, but from similar products too (although this latter protection was rarely applied in the past).

The graph below demonstrates the interplay among the two protections for orphan medicines, with the 2-year market launch conditionality (Figure 26):

Figure 26 – interplay RDP and market exclusivity for standard and HUMN orphan products



Other points of coherence between the general and orphan medicines legislation are listed below. Together they create an integral system through:

- The revision of procedures for accelerated development and assessment of medicines for major public health needs taking into account novel technologies, in particular, the implementation of the PRIME scheme.
- Upstream cooperation among actors of the pharmaceutical lifecycle which foresees the reinforcement of mechanisms for cooperation and coordination between the regulatory authorities, Health Technology Assessment (HTA) authorities and payers building on the possibilities of the new HTA rules.
- Simplification of procedures and reduction of burden for generic/biosimilars. For example, currently it is not possible to apply for a marketing authorisation for a generic/biosimilar before the orphan market exclusivity period is over (i.e. 10 years after obtaining the marketing authorisation) whereas for other medicines this is possible when the data protection expires and before expiry of market protection. In the new system, application for marketing authorisation for generic

or biosimilar medicines will become possible *before* the expiry of market exclusivity.

- Future-proofing of the legislation, meaning its adaptation to rapid technological changes, including personalised medicine, will benefit patients as described in section 8. This will allow the full use of opportunities brought by gene therapies and personalised medicine which in many cases may concern medicines for rare diseases.

In the case of transferable exclusivity vouchers (TEVs), at first glance, there may seem to be incoherence between the two regimes. The conclusion in the Impact Assessment for the revision of the legislation on medicines for rare diseases is that TEVs can be considered as an ineffective incentive to generate innovation, whereas in the case of antimicrobials they may be a more plausible incentive if applied strictly.

In fact, this different conclusion stems from the 'special' character of the antimicrobial sector and the particularity of the market failure in this case. Both cases relate to incentivising products for a limited number of patients (rarity of the disease in the first and desire to use the new antimicrobial as little as possible in the second). However, contrary to rare diseases, the societal risk of AMR (which potentially concerns the whole population and not just a few patients) and its actual and potential economic consequences combined with the very limited pipeline of antimicrobials with a new mechanism of action suggests that the advantage of having TEVs specifically for novel antimicrobials as an 'insurance policy' against resistant antimicrobials may surpass the disadvantages of the high costs for the very limited number of TEVs that are likely to enter the market.

Study in support of the evaluation and impact assessment of the EU general pharmaceuticals legislation

Evaluation Report

Written by Technopolis Group
For the Directorate General for Health and Food Safety
June 2022

DG SANTE

EUROPEAN COMMISSION

Directorate General for Health and Food Safety
Directorate D – Medical Products and Innovation
Unit D.1 – Medicines: policy, authorisation and monitoring

E-mail: sante-pharma-policy@ec.sante.eu

European Commission
B-1049 Brussel

PROJECT TEAM

Peter Varnai, Anoushka Davé, Paul Simmonds, Marisa Amato, Rebecca Babb, Ruth Dixon, Thyra de Jongh, Tatiana Paredes, Maialen Perez, Liana Petrosova, Bruno Raabe, Anneloes de Ruiter (Technopolis Group); Florent Pelsy, Maxime Moulac (Milieu Law & Policy Consulting); Aukje Mantel-Teeuwisse, Lourens Bloem, Wouter Boon, Marieke De Bruin, Jarno Hoekman, Kevin Klein, Pieter Stolk, Rick Vreman (Utrecht University); Timothy Pang, Ben Folwell (Citeline Custom Intelligence); Florian Szücs (Vienna University of Economics and Business); and Wim Spit (Ecorys BV).

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GLOSSARY

Term or acronym	*Meaning or definition*
ADR	Adverse drug reaction
AMR	Antimicrobial resistance
API	Active Pharmaceutical Ingredient
ATC	Anatomical Therapeutic Chemical code
ATMP	Advanced therapy medicinal product
BSSD	Basic Safety and Standards Directive
BTC	Blood, tissue and cell
CHMP	Committee for Medicinal Products for Human Use
CMA	Conditional marketing authorisation
CMC	Chemistry, Manufacturing and Control
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures
CMO	Contract Manufacturing Organisations
CP	Centralised authorisation procedure
DCP	Decentralised authorisation procedure
EEA	European Economic Area
EFTA	European Free Trade Association
EMA	European Medicines Agency
FDA	United States Food and Drug Administration
GDP	Good Distribution Practices
GMP	Good Manufacturing Practices
GDPR	General Data Protection Regulation
GMO	Genetically modified organism
HTA	Health Technology Assessment
ICSR	Individual case safety reports
IP	Intellectual property
MAH	Marketing authorisation holder
MRP	Mutual recognition procedure
MS	Member State
NAS	New active substances

NCA	National Competent Authority
OPC	Open public consultation
PDMP	Plasma Derived Medicinal Product
PRAC	Pharmacovigilance Risk Assessment Committee
SDG	Sustainable Development Goal
SME	Small and medium enterprises
SPC	Supplementary Protection Certificate

ABSTRACT

The most recent comprehensive revision of the EU general pharmaceuticals legislation took place in 2004. In the intervening decades, the global pharmaceutical sector, technological approaches and societal focus have changed. The new Pharmaceutical Strategy for Europe provides a framework for new developments as part of the Commission's vision to build a stronger European Health Union. This strategy calls for an evaluation of the performance of the current regulatory system and targeted revision of the general pharmaceutical legislation. The report summarises data and analyses to support the evaluation of the legislation, notably Directive 2001/83/EC on the Community code relating to medicinal products for human use and Regulation (EC) 726/2004 laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing a European Medicines Agency.

The study followed the Better Regulation guidelines, to develop an intervention logic and a baseline; assess the effectiveness, efficiency, relevance, coherence and EU added value of the legislation; consider lessons learnt from the COVID-19 pandemic in relation to the functioning of the pharmaceutical system; and draw conclusions on the evidence gathered to support future policy decisions.

EXECUTIVE SUMMARY

Study scope and objectives

The study in support of the evaluation focussed on Directive 2001/83/EC on the Community code relating to medicinal products for human use and Regulation (EC) No 726/2004 laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing a European Medicines Agency, i.e., the general pharmaceutical legislation. The relevant time period for the evaluation is following the completion of the comprehensive revision of the legislation in 2004, from the year 2005 until end of 2020, and covers relevant trends and developments for the development, authorisation, manufacturing, supply, and monitoring of medicines. The years between 2000-2005 served as a baseline for the evaluation. The geographical scope of the evaluation was the European Economic Area, however comparisons with the other jurisdictions such as the US, Australia, Canada, Israel, China, Japan and South Korea were also made where relevant and feasible.

The goals of the study were specifically:

1. To assess, in line with the Better Regulation guidelines, the effectiveness, efficiency, relevance, coherence and EU added value of the legislation;
2. To assess the performance of the legislation during the COVID-19 crisis in relation to the functioning of the pharmaceutical system and consider the lessons learnt from the pandemic;
3. To draw conclusions on the evidence gathered to support future policy decisions.

Methodological approaches and limitations

A mixed quantitative and qualitative approach was applied to collect and analyse data in the study. It included peer-reviewed literature and policy document review to gather existing knowledge base and served as a source of facts and figures; secondary data analysis, including statistical, econometric and trend analysis. In addition, case studies were developed that focus on specific issues and illustrate linkages and mechanisms behind trends observed in the data. Finally, extensive stakeholder consultations were conducted and resulting primary data was analysed from the feedback for the consultation on the Roadmap/Inception Impact Assessment and public consultation, targeted surveys, interviews and an evaluation workshop for stakeholders. Stakeholder groups consulted included public authorities, civil society and patient organisations, healthcare professionals and their associations, academic and public research organisations/experts and industry.

There have been a number of limitations that affect the robustness of findings. First, effects are linked to a complex multi-factorial evidence base and stakeholders were often unable to break down observed effects to drivers. This was particularly the case for providing quantitative information linked to the costs and benefits (efficiency) of the legislation. Second, the broad scope of the general pharmaceutical legislation inherently linked it to a large number of specialised pharmaceutical legislations and other more general EU rules and laws that have been added and periodically amended over the years. These confounding external factors influenced primarily the relevance, effectiveness and efficiency of the legislation. In addition, many businesses operate globally with functional teams that comply with and report to authorities in multiple jurisdictions and therefore they were not able to isolate the effects of the EU legislation. Third, due to the extended time period in scope for the evaluation, many stakeholders consulted were not able to provide historic perspective on the situation before 2005, or the early years of the implementation of the 2004 legislative revision. Further, quantitative data definition and data collection approaches changed over time making it challenging to conduct a continuous trend analysis.

Background to the intervention

The overarching need of a general pharmaceutical legislation was to guarantee a high level of public health throughout Europe. This meant that safe, high quality and effective medicines needed to be available and accessible to patients regardless of the member state in which they resided. The 2004 revision of the general pharmaceutical legislation envisioned four main, high-level objectives:

1. Ensure quality, safety and efficacy of medicinal products. This means a robust authorisation system, surveillance and supervision are in place along the entire medicinal product lifecycle, including post-authorisation monitoring and pharmacovigilance procedures.

2. Ensure access to medicines. Health protection can only be effective if patients have equitable access to medicinal products as early as possible after authorisation.
3. Ensure competitive functioning of the EU internal market. Competition across medicine developers is expected to bring ever more innovative and effective medicines to meet the needs of patients in all member states (both original branded forms and those that are no longer under patent protection, i.e., generic versions).
4. Ensure attractiveness in the global context. Medicine development is a global endeavour, and it is important that Europe has a legislative framework that is globally attractive to medicine developers.

More specifically, these high-level objectives were expected to be achieved through a number of more specific objectives which were mutually reinforcing a more systemic view:

Accommodate innovation. This means that the legislative system is ready for the new scientific and technological developments that underpin innovative and effective products. Here innovation comprises not only new molecular entities but also adding value (follow-on innovation), repurposing existing medicines and developing biosimilar products.

Reduce administrative burden, improve adaptability of regulatory environment. This specific objective responds directly to the need for all medicine developers (including generic manufacturers) to navigate the regulatory landscape with minimum administrative burden (cost and time) and, as noted above, accommodate new scientific and technological developments.

Reduce disparities and duplication of efforts. Historically, European countries had differing rules and processes that added complexity and resulted in duplicated efforts. Harmonisation and standardisation were promoted to reduce duplication, improve certainty and transparency to allow a level playing field for medicine developers across European MSs and transparent information access to patients.

Facilitate free movement of medicinal products. According to the concept of the internal EU single market, products should be traded freely across the Union. This objective aims to facilitate free trade for medicinal products through greater harmonisation of processes.

Baseline

In the increasingly globalised environment and pharmaceutical practices in the 1990s, the European pharmaceutical sector was losing competitiveness to the US. Fragmented EU member state policies did not result in the level of scientific interaction between industry and public or private research organisations that would have been necessary for industry to successfully exploit the latest scientific results. European pharmaceutical companies struggled to advance in innovative areas such as biotechnology. In addition, European companies tended to operate exclusively in their protected national markets which did not provide strong incentives to adopt innovation and globalised business strategies.

The European pharmaceutical system had two major routes to authorise medicines since 1995: the historic national authorisation route (and the related mutual recognition procedure, MRP) and a centralised route via the (now named) European Medicines Agency. Nevertheless, the MRP system was seen as less successful in achieving harmonisation as some Concerned Member States continued to evaluate marketing authorisation applications, sometimes raising concerns that were unaligned with the recognition principle. Regulatory data protection periods differed under the two approval systems and across national systems, which led to differences in availability of innovative products on national markets and lowering pharmaceutical companies' willingness to invest in incremental research.

The continued EU enlargement also contributed to the need to establish an integrated environment for pharmaceuticals, as differences across the new member states would have amplified the problems of fragmentation and disparity.

Evaluation findings

Effectiveness

The legislation has been most effective with regard to the objective of safeguarding public health and least effective in terms of ensuring access to medicines and addressing medicine shortages,

according to overall stakeholder opinion. Industry identified two areas where the legislation was deemed the least effective: minimising inefficiencies and administrative burden of regulatory procedures; and improved global competitiveness of the EU pharmaceutical industry.

Quality, safety and efficacy of medicinal products

One of the major enablers for achieving this objective is the centralised procedure (CP), which has allowed effective and robust authorisation of medicines at EU level, together with decentralised procedure/mutual recognition procedure (DCP/MRP), pre-authorisation scientific advice and other services provided by EMA. These achievements have improved quality standards and have ensured safe and efficacious medicines are available to the EU population.

Stakeholder consultations also highlighted some areas for improvement, including the assessment of microbiome products, GMOs and environmental risk as well as better accommodation of bedside and decentralised manufacturing in the legislation or related guidance.

Attractiveness in the global context

The 2004 revision was an important step forward in ensuring a coherent and attractive regulatory system for developing pharmaceuticals, in response to increased scientific and technological complexity of medicinal products and EU enlargement. The centralised procedure was remarked that allows developers to make the first steps to EU market access in an integrated fashion, which increases the EU's attractiveness as both market and location for pharmaceutical development and manufacturing. The EU has also been a global leader in setting up a process for licensing biosimilars, which encourages innovation and submitting market application in the EU.

Nevertheless, the USA remains the largest global market for pharmaceuticals, more than twice the size of the EU market which has the second largest share of the global market. Several industry participants confirmed that the USA remains the preferred jurisdiction for developers to file innovations. Reasons for these preferences include differing data requirements, greater opportunity for direct interaction on scientific advice and the need to interact with multiple EMA committees in complex cases. New active substances authorised by all agencies are largely submitted to the US FDA first and followed by submission to the EU. However, the proportion of US FDA-authorised substances not authorised by EMA decreased over time, which shows that the EU system is globally attractive. In particular, the legislation has proven flexible enough to accommodate many developments and innovations in the pharmaceutical sector. There has been a growth in the number of innovative medicines, including technologically innovative medicines (e.g. ATMPs) and those addressing unmet medical needs (e.g. through PRIME and conditional marketing authorisation routes).

There are areas where the legislation has not been fully able to accommodate emerging technological developments as readily, such as combination products/borderline cases with medical devices or substances of human origin, digitalisation and new manufacturing methods. It was a common view in the consultations that one of the reasons for this problem is the lack of coherence in certain areas of the EU regulatory system, which can make it less attractive for developers, in particular for SMEs.

Access to medicines

The 2004 revisions expanded the scope of the centralised procedure and harmonised other procedures and rules to improve access to medicines across the EU. Access however remains uneven across the EU, even for medicinal products that have been approved through the EMA's centralised procedure. Perhaps it is not surprising as access involves multiple criteria[1], some of which are outside the scope of the EU legislation. The data for total assessment times by EMA show a notable improvement between 2005-2010, which then increased gradually over the following period. In comparing the EMA and FDA assessment times, EMA average assessment times are shorter than those of the FDA for the period up until 2015, beyond which the situation reversed.

[1] Access is defined by fulfilment of the following criteria: 1) a medicine has been (conditionally or fully) approved for marketing in the country, 2) has been placed on the market by the marketing authorisation folder, and 3) is made available to patients as part of (partially) reimbursed care.

Stakeholders reported inefficiencies related to differing interpretation and implementation of the legislation and other relevant regulations and directives at the MS level which has led to delayed and unequal access across Member States.

Affordability

The affordability of medicines is an important factor for national health systems and patients, and it also has relevance to the profitability of the pharmaceutical industry. It is remarked that pricing and reimbursement decisions are based on national assessments of cost-effectiveness and thus in the remit of national authorities. Nevertheless, beyond intellectual property protection (conferred by patents and supplementary protection certificates), regulatory protection (i.e., data exclusivity and market protection) are also granted at the EU level to incentivise and reward pharmaceutical innovation. While the regulatory protection periods are now harmonised in the EU, the multiple possible protections can create a complex system.

An analysis of a sample of products of EU4 countries (France, Germany, Italy and Spain) with protection expiry between 2016-2024 shows that two thirds of the products are protected by intellectual property rights from generic competition, while one third of the products are protected by regulatory protection.

Medicine prices vary significantly between EU member states, and pharmaceutical spending is the third biggest cost element in healthcare spending at roughly 1.5% of the EU's GDP. Average spending on pharmaceuticals however remained stable in the EU over the last 20 years at about 20%. Spending levels and trends also depend on therapeutic areas; spending on oncology products increased fastest, while spending on cardiovascular products decreased over the same period. Understanding spending in hospital settings is more complex, however, there are indications that pharmaceutical spending in hospital settings has been rising faster.

Our analysis of top selling medicinal product sales data indicates that branded product prices drop on average by one third of the price level prior to generic entry. This is the highest level of decrease among comparator countries, and similar to that in Australia and Korea. The discount of the corresponding generic products (compared to the price level of branded equivalent prior to generic entry) is even larger in the EU and steadily increased since 2007 from 50% to 65%.

Medicine shortages

Medicine shortages is a key issue impacting on access to medicines and ultimately public health. Health professionals noted that the current legislation has not been effective in addressing the issues of the medicine shortages as evidenced by rising shortage notifications over the last 10 years. However, there may be other factors contributing to the increase, for example, there are more countries tracking and reporting shortages, and or doing so more effectively. The dominance of notifications due to 'quality and manufacturing' issues can be seen as an example of the legislation having been successful in increasing the observance of manufacturing standards. The implication is that, while the legislation has helped in creating more insight into the scale and the prevalence of medicine shortages, it has not yet been able to address sufficiently the reasons behind the shortages occurring or to alleviate their impact. Stakeholders, particularly industry and NCAs, report that generic medicines are particularly at risk of shortages, given the higher relative fragility of their supply chains.

Accommodating innovation

The legislation has provided a regulatory system which has facilitated innovation across the product lifecycle according to stakeholder interviews. The centralised procedure, the creation of the EMA, the scientific advice procedures and overall harmonisation of quality and manufacturing rules were cited as some of the main enablers for accommodating innovation.

Some of the shortcomings stakeholders pointed to include addressing and supporting generic and biosimilar innovation, unmet medical needs, and development of antimicrobials. Stakeholder groups concurred that digitalisation and emerging science and technology developments have not been adequately integrated in the current regulatory system. Most stakeholders agreed that the legislation and related guidelines do not provide sufficient clarity for companies and national regulators when it comes to combination products (i.e. medical devices that also contain medicines), use of real-world evidence for clinical trials and medicinal products consisting of or containing GMOs.

Competitiveness of EU pharmaceutical industry

The ever-increasing need for innovation in the pharmaceutical sector has led to an increase in total R&D expenditure in the EU, doubling since 2000 to more than €40bn in 2019, albeit no significant change can be attributed specifically to the implementation of the 2004 revisions of the legislation. The EU has a strong second position globally, especially together with its close neighbours, the UK and Switzerland, that are part of the European biopharmaceutical innovation ecosystem through cross-country collaborations and movement of skilled professionals and capital. Nevertheless, R&D investment in the EU has remained significantly lower that than in the US (€74 billion in 2019).

Competitive functioning of the EU internal market

There are differing views among stakeholders as to what the internal EU market for pharmaceuticals is. Some stakeholders (e.g. civil society, healthcare professionals and public authorities) disputed the idea that there is a single EU market for medicines. Their view is that there are multiple national/regional markets in practice. It is also worth noting that markets can only be understood for individual therapeutic areas as there is no competition across therapeutic areas. There is agreement across the various stakeholder groups that competition is suboptimal.

Nonetheless, many stakeholders agreed that the legislation has been beneficial for increasing competition in the pharmaceutical sector of the EU by facilitating generics and biosimilar entry in the market, particularly through the Bolar exemption.

The EU has been an early adopter of biosimilars and delineated an authorisation pathway for biosimilars much before any other country. The biosimilar pathways are seen as success increasing competition with the originator and facilitate access of biosimilars to patients.

Efficiency

Most stakeholders were unable to provide quantitative estimates of the costs and benefits associated with the 2004 revisions of the legislation. This limited number of observations was augmented by data from studies, where possible, and we have therefore provide large ranges for the monetary estimates of costs and benefits.

The 2004 revision is likely to have resulted in a net increase in regulatory costs to society on the order of €1.1bn-€1.8bn (over 15 years). The higher costs are the result of the higher standards set and the associated additional compliance and regulatory costs. There have also been benefit gains in terms of reduced costs for MAHs, the EMA and NCAs, which sum to €1.2bn-€1.5bn, largely offsetting the additional costs of increased information requirements and pharmacovigilance activities.

The 2004 revision is also widely believed to have resulted in more innovative medicinal products and a higher quality regulatory system, which is likely to have resulted in a positive health impact for patients treated with such products, which would otherwise not have been available, or would have been available later in time. We have estimated this additional health impact at 25-30 new innovative medicines, in total; which amounts to €4.8bn-€17.2bn in monetised benefits, using WHO guidelines on valuing QALYs. The valuation of health impacts is widely accepted to be deeply challenging and was carried out at an aggregate level, however, even working with the lower bound estimate of health impacts and cost savings (€6bn) and the upper bound of the estimated additional costs (€1.8bn), the 2004 revisions have delivered a positive overall social return.

This economic analysis resonates with feedback from stakeholders overall, where the overall balance of opinion is positive: the costs of the revisions are judged to have been proportionate to the benefits. The overall positive opinion as to the cost-effectiveness of the legislative changes, looks different across stakeholders. Industry and public authorities are strongly positive on the overall balance of costs and benefits, whereas health systems and – in particular – patient groups are slightly negative overall. The latter consider the legislation has been strongly beneficial to industry, with the revisions offering valuable incentives that have supported investment in innovative medicines but have increased prices for those products. They are very much less positive about the balance of costs and benefits from the patient's perspective, expressing concerns about affordability, uneven access, unmet medical needs, and medicines shortages.

Coherence

In terms of internal coherence, the legal analysis and literature review on the legislation has identified overlaps, contradictions, or other inconsistencies within or between the Directive and the Regulation.

There are several in-built mechanisms to ensure an adequate articulation between the general pharmaceutical legislation and the specialised pharmaceutical frameworks. Nevertheless, some potential issues of coherence were identified, for example due to differing national rules on the conduct of trials with children may still delay the completion of a paediatric investigation plan (Paediatric Regulation) and for orphan medicinal products, generic competitors can only submit an application for marketing authorisation at the end of the 10-year protection period (Orphan Regulation).

There are several pieces of legislation not included in the specialised pharmaceutical legislation whose implementation can impact on several objectives of the general pharmaceutical legislation. Specific points were identified in linked legislations on health matters, including in the EMA fees Regulation, BTC legislation, Medical Devices Regulation, Health Technology Assessment Regulation, Cross-border healthcare Directive, GMO (Genetically Modified Organisms) legislation. Additional aspects were analysed in linked legislations not directly linked to the health sector, namely, SPC legislation, Unitary Patent protection, Data protection laws, drug precursor legislation, REACH Regulation, Environmental Quality Standard Directive, and EU Competition law.

In terms of coherence in implementing parts of the legislation, two key issues have been identified. First, the interpretation and timing of implementation of the 'Bolar' provision by member states. Second, the implementation and practice of hospital exemption that shows variations in the ways quality, safety and efficacy standards are implemented and controlled across member states for ATMPs.

How did the EU intervention make a difference?

The legislation provided a robust framework enabling harmonisation of regulations, incentives, standards, administrative requirements, and procedures for pharmaceuticals across the EU, according to stakeholders. These centralised and coordinated harmonisation measures across the medicine lifecycle simplified the regulatory system for medicine developers and reduced duplication of efforts across member states.

Within interviews, stakeholders commonly cited the creation of the European Medicines Agency (EMA) as one of the biggest achievements of the legislation. Stakeholders regarded EMA as a key actor in the unification and coordination of the regulatory system across the EU. The centralised procedure has been particularly valuable for smaller member states without the necessary resources and expertise to establish their own systems. The pooling and coordination of scientific resources under a common set of rules and practices has helped foster a common understanding across MSs on how medicinal products are evaluated and approved to a high standard and dealing with safety concerns in a consistent way. Industry stakeholders pointed to increased cooperation between member states and public authorities and highlighted successful collaboration of EMA with national competent authorities that has led to the optimisation of their resource use.

Furthermore, since the establishment of EMA, transparency on how the regulatory system works and decisions are made has greatly improved – thus building trust and consistency across the EU regulatory system. EMA publications of European public assessment reports (EPARs) and guidance documents were cited as a reason for the increased flow of transparent information.

EU action during COVID-19 crisis was a particularly value added intervention. EU level action enabled quicker and concerted action compared to what MSs would have been able to achieve independently. Stakeholders commonly cited this was made possible because of regulatory flexibilities and optimisations enabling resources, capacities, expertise, and IT capabilities to be rapidly mobilised across EU.

There was consensus that the legislation has struck the right balance between action at EU level and national action and highlighted the added value of EU-level coordination and cooperation to develop best practices.

Is the intervention still relevant?

The objectives of the general pharmaceutical legislation remain valid after 15 years despite the introduction of multiple specialised legislations and several amendments of those. However, the legislation has limited provisions, mandate and specific action available to ensure that authorised medicines are launched in all member states and thus ensure equitable access to those for citizens across the EU. Therefore, the relevance of the legislation to equitable access to medicines is low.

Looking into the future, new objectives would need to be considered for the legislation to remain relevant in the face of the megatrends identified by the EU's Joint Research Centre. This includes the readiness and adaptability of the legislation to respond to technological developments and rapidly increasing presence of digitalisation in new tools generating regulatory evidence and medicinal products preventing, diagnosing and targeting diseases. Continued relevance also involves providing targeted incentives to the development of those medicinal products that respond to high unmet medical needs, for example for therapies against antimicrobial resistant infections.

The recognition of the increasingly complex and advanced therapies as medicinal products within the legislation is also important to ensure continued relevance of the legislation to permit authorisation of those products in a streamlined manner for all manufacturers, small to large, commercial or otherwise.

Conclusions

The general pharmaceutical legislation is a successful EU intervention in the sense that it achieved all four high level objectives to some extent. The objective to ensure quality, safety and efficacy of medicinal products was achieved to the largest extent, while that of ensuring access to medicines was achieved to a limited extent. The objectives of ensuring competitive functioning of the EU internal market and attractiveness in a global context were achieved to a moderate extent. With the needs and problems that the 2004 revisions were addressing still remaining relevant, the objectives of the legislation and its revision also continue to remain relevant for the future.

A robust and flexible authorisation system was developed in Europe taking advantage of harmonised processes through the centralised procedure for innovative medicines requiring pooled European scientific expertise; while decentralised procedures at national level available for smaller companies and generic producers with distinct business models. In addition, post-marketing monitoring and reinforced inspections of manufacturing and distribution created a consistent system along the lifecycle of medicines. These elements contributed strongly to the stated objective of ensuring quality, safety and efficacy of medical products in Europe.

The system includes a predictable incentives framework (8+2 years of regulatory data and market protection period) that has kept Europe an attractive market for medicine developers and allowed innovative medicines to be available to national health systems. However, this does delay market entry of generic products, affecting affordability of medicines and national health budgets. On the other hand, the Bolar exemption has allowed quicker generics entry, but since the implementation of the exemption varies, the benefits are also variable. The creation of a delineated authorisation pathway for biosimilars in Europe before any other jurisdictions, has made Europe a leader in this space, allowing the launch of biosimilars on the EU market and thereby increasing access for patients, choice for health services and providing cost savings for national health system. Yet, there is room for further improving the uptake of biosimilars across EU member states.

It is important to note however that the availability of innovative medicines does not lead to equitable access to those across member states, another stated objective of the legislation. In effect, the relevance of the legislation is rather limited with regard to access, as companies make decisions on market launch while national health systems retain clear responsibility over providing their chosen healthcare provision (including medicinal products) to their population and likewise for the decision to pay for those. Nevertheless, the legislation was not able to steer market launch decisions of companies and access to medicines primarily in smaller member states and those with lower per capita healthcare budgets. Access thus remains a real problem for many to guarantee a high level of public health.

The European pharmaceutical industry sector remains second behind the US even though revenues have increased. Similarly, R&D investment has increased in absolute terms but not as fast as in USA or Japan. The US remains the jurisdiction of choice for filing marketing authorisation

applications for new active substances, but the EU has the second destination for filing and more substances are being authorised by the EMA less than 1 year after the FDA.

The legislation is well-framed, internally coherent and has clear EU added value. However, external coherence has become a challenge in a changing EU regulatory landscape. Emergence of new technologies and borderline cases (that potentially sit between two or more legislations) cause inconsistencies/uncertainties such as the coverage of GMO requirements, environmental challenges and new manufacturing methods along with definition of products e.g. ATMPs, radiopharmaceuticals and medical devices.

Lessons learned

The objectives of the general pharmaceutical legislation remain valid after 15 years. As discussed, not all objectives have been fully met through the 2004 revisions of the legislation and new approaches are needed to address those challenges. However, these are complex issues that the legislation in itself may not be able to solve effectively.

Improved coherence with other specialised health legislations is required to remove uncertainty and improve consistency of interpretation. In addition, improved coherence with other wider EU legislations is required to reduce tensions and improve synergies between legislations, increasing the likelihood of impact in terms of public health, environmental sustainability, digitalisation, etc. This will ensure a more systemic fit of the general pharmaceutical legislation in the wider EU policy framework.

Looking into the future, new objectives will need to be considered for the legislation to continue to remain relevant. This includes the readiness and adaptability of the legislation to respond to technological developments, e.g., in new manufacturing methods, and rapidly increasing presence of digitalisation in new tools generating (real world) regulatory evidence and medicinal products preventing, diagnosing and targeting diseases. Continued relevance also involves providing targeted incentives to the development of those medicinal products that respond to high unmet medical needs, for example for therapies against antimicrobial resistant infections. The recognition of the increasingly complex and advanced therapies as medicinal products within the legislation is also important to ensure continued relevance of the legislation to permit authorisation of those products in a streamlined manner for all manufacturers.

Many lessons have been learned from the recent experience of medicine developers and public authorities having acted under the pressure of the ongoing COVID-19 pandemic. It has demonstrated that there is room for flexibility to adapt regulatory processes and accelerate product development and authorisation processes, including use of remote processes for source data verification, virtual audits and monitoring. This would reduce administrative burden on medicine developers and release capacity for regulatory authorities. EMA has also adapted its governance model to respond to the scientific, regulatory and operational challenges which can serve as a blueprint not only for future emergencies but for a more fit for purpose system as safety and efficacy of increasingly complex and advanced therapies will need to be assessed. It is however noted that EMA has limited resources and its expertise and capacity need to be expanded in order to progress complex dossiers at pace and keep up with the US FDA, where relevant, and do so without compromising safety and quality of authorised medicines.

The pandemic also highlighted factors causing shortages such as over-reliance on one single or very few foreign suppliers for some essential APIs. This might be mitigated through diversification of suppliers. Collaboration between industry and regulators (especially EMA) during the pandemic on stocks and shortages, to provide scientific advice and to generally expedite the medicine development process demonstrated that different interests can be usefully aligned. This however needs to happen under public scrutiny and transparency.

1 INTRODUCTION

This is the final report for "The study in support of the evaluation and impact assessment of the EU general pharmaceutical legislation" that was commissioned by the Directorate-General for Health and Food Safety and was carried out by Technopolis Group with support of Ecorys BV, Milieu Law & Policy Consulting, Utrecht University (Centre for Pharmaceutical Policy and Regulation & Innovation Studies Group) and Informa Pharma Custom Intelligence.

This report first elaborates the purpose and scope of the evaluation along with the methodological approach and its limitations. Next, it provides a background to the intervention and how the situation evolved over time. It then provides the findings of the evaluation first summarised as a high-level narrative before providing responses to individual evaluation questions per evaluation criterion. Finally, we describe the key conclusions from the evaluation.

1.1 Purpose and scope of the evaluation

The evaluation focussed on Directive 2001/83/EC on the Community code relating to medicinal products for human use and Regulation (EC) No 726/2004 laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing a European Medicines Agency, i.e., the general pharmaceutical legislation (in the following "legislation"). The goals of this study were specifically:

- To assess, in line with the Better Regulation guidelines, the effectiveness, efficiency, relevance, coherence and EU added value of the legislation;
- To assess the performance of the legislation during the COVID-19 crisis and consider the changed circumstances and the lessons learnt from the pandemic in relation to the functioning of the pharmaceutical system;
- To draw conclusions on the evidence gathered to support future policy decisions.

1.2 Scope of the evaluation

The evaluation covers the core of the legal scope of the general pharmaceutical legislation and it includes aspects of the specialised product groups, i.e., advanced therapy medicinal products, medicines for children and medicines for rare diseases, insofar these are covered by the general pharmaceutical legislation. The specialised pharmaceutical legislations themselves were not in scope for the evaluation.

The evaluation only partially assessed the following provisions (i.e., in relation to the objectives of the evaluation) that have been recently added to the corpus of the general pharmaceutical legislation due to their relative novelty:

- Amending Directive 2010/84/EU and 2012/26/EU: Pharmacovigilance;
- Amending Regulation (EU) No 1235/2010 and 1027/2012: Pharmacovigilance;
- Amending Directive 2011/62/EU Falsified medicinal products, with exception of the provisions relating to active pharmaceutical ingredients (APIs) and brokering of medicinal products.

The relevant time period for the evaluation is from the year 2005 until end of 2020. This is because 2004 marked a significant amendment to the legislation[2], with implementation starting in the following year. The 15-year period for the evaluation was used to illustrate trends and developments over time that were relevant for the development, authorisation, manufacturing, supply, and monitoring of medicines. However, the evaluation covered all key aspects and developments that are relevant to the current performance of the EU legislation, including elements that had not been directly addressed by the legislative changes in 2004. The years between 2000-2005 leading up to the implementation of the revised legislation served as a baseline for the evaluation.

The geographical scope of the evaluation was the European Economic Area, i.e., EU28 and three EFTA states, however comparisons with the other jurisdictions such as the US, Australia, Canada, Israel, China, Japan and South Korea were made where relevant and feasible (e.g., in the comparative legal analysis and quantitative secondary data analysis).

[2] Official Journal of the European Union publication date of 30 April 2004.

1.3 Methodological approaches and limitations

The evaluation assessed the general pharmaceutical legislation based on the five overarching evaluation criteria of effectiveness, efficiency, coherence, relevance and EU added value. To that end, a layered list of evaluation questions was drafted per evaluation criterion using the Commission's list from the Terms of Reference as a starting point. An evaluation matrix was developed to provide a framework for answering the evaluation questions (see Annex II). The matrix cross-references evaluation questions to the relevant judgement criteria, list of indicators and analytical approaches i.e., methods/tasks.

In terms of **methodology**, a mixed quantitative and qualitative approach was applied drawing on multiple methods (see Annex I). It included peer-reviewed literature and policy document review to gather existing knowledge base and served as a source of facts and figures; secondary data analysis of over 50 macro indicators relevant to industrial & economic competitiveness, through research & innovation, to access, affordability and single market effects, including statistical, econometric and trend analysis in the EU, compared to data from other jurisdictions. This information is available in the Analytical report. In addition, case studies were developed that focus on specific issues and illustrate linkages and mechanisms behind trends observed in the data. Finally, extensive stakeholder consultations were conducted and resulting primary data was analysed from the feedback for the consultation on the Roadmap/Inception Impact Assessment and public consultation, targeted surveys, interviews and an evaluation workshop for stakeholders. Stakeholder groups included public authorities, civil society and patient organisations, healthcare professionals and their associations, academic and public research organisations/experts and industry.

There have been a number of **limitations** that affect the robustness of findings. First, effects are linked to a complex multi-factorial evidence base and stakeholders were often unable to break down observed effects to drivers of those effects and link those to specific legislative measures in scope. This was particularly the case for providing quantitative information linked to the costs and benefits (efficiency) of the legislation.

Second, the broad scope of the general pharmaceutical legislation inherently linked it to a large number of specialised pharmaceutical legislations and other more general EU rules and laws that have been added and periodically amended over the years in scope of the evaluation. These confounding external factors influenced primarily the relevance, effectiveness and efficiency of the legislation. In many cases, stakeholders provided information more directly attributable to these other legislations rather than to the legislation in scope for the evaluation. In addition, many businesses operate globally with functional teams that comply with and report to authorities in multiple jurisdictions and therefore they were not able to isolate the effects of the EU legislation.

Third, due to the extended time period in scope for the evaluation, many stakeholders consulted were not able to provide historic perspective on the situation before 2005, or the early years of the implementation of the 2004 legislative revision. Staff turnover in organisations over time and limited institutional memory also contributed to limitations in data collection. Many businesses underwent business development activities including acquisitions, mergers, initiation of new research areas or discontinued development programmes, which all result in apparent changes not attributable to the legislation.

Fourth, some stakeholder groups (especially the civil society and public authorities) found it challenging to mobilise internal resources to provide information, data and evidence across all evaluation dimensions and data collection channels during the data collection period of the study. It should also be noted that stakeholder consultation took place during an intense wave of the coronavirus pandemic in Europe. To make sure that views from across the stakeholder groups were included, the study team used a purposive sampling frame for interviews and workshops to allow good coverage of different member states (MSs) and stakeholder types (e.g., a spread across associations and individual companies, generics companies and originators, large pharma and SMEs in industry; national competent authorities [NCAs] and payers among public authorities, etc.). To mitigate response rate bias for the targeted survey and open public consultations, results were presented by stakeholder group or weighted in calculations.

Further, quantitative data definition and data collection approaches changed over time making it challenging to conduct a continuous trend analysis over the 2000-2020 time period. Moreover, data collection and indicators are not uniform across all countries. As such, the extent to which

robust analysis and interpretation is possible especially for comparisons across different jurisdictions and even MSs is limited depending on the comparability and (un)availability of data. The difference-in-difference statistical approach was used as part of the mitigation measures for this problem where possible.

As a result of the limitations described above, both qualitative and quantitative data collected during the evaluation show large variations of quality across stakeholder groups. Extensive data cleaning and data verification were applied to ascertain that data provided meet the inclusion criteria of the study (i.e., the answer is relevant to the question posed). Much of the quality data collected are linked to more recent years and therefore direct attribution of these effects to the 2004 revision of the legislation remains limited. In terms of qualitative data collected through open questions in the targeted survey and open public consultation (OPC) as well as interviews, data quality and quantity were affected by a variety of factors including the number and nature of topics covered, time available for responses (e.g., 90 minutes for interviews) and domain expertise of respondents. Moreover, stakeholder groups were not homogenous but comprised a variety of different stakeholder types. Therefore, it was not possible to determine the consensus view or explanation for some topic areas.

2 BACKGROUND TO THE INTERVENTION

2.1 Description of the intervention and its objectives

An intervention logic for the 2004 revision of the legislation was not formally developed in 2001 when the legislative review of the general pharmaceutical legislation was initiated. This legislative review was a formal requirement of Article 71 of Regulation (EEC) No 2309/93 to analyse the achievements of Regulation (EEC) No 2309/93 and Directive 75/319/EEC, Chapter III.

However, a robust evaluation requires an intervention logic describing the objectives and impact pathways envisioned for the intervention. An intervention logic was therefore developed as part of the current study building on the draft model provided in the Terms of Reference. It is important to emphasise that an intervention logic shows how the intervention was expected to work by the legislators when it was introduced and not how it worked in practice, which is the subject of this evaluation. A diagram depicting the intervention logic i.e., the relationship between the objectives, actions, results and impacts of the intervention is shown in Figure 1.

The overarching need of a general pharmaceutical legislation was to **guarantee a high level of public health throughout Europe**. This meant that safe, high quality and effective medicines needed to be available and accessible to patients regardless of the MS in which they resided. This was particularly relevant as the European Union continued the enlargement process beyond 2004. Moreover, the revision recognised that development of medicinal products was a scientifically and technologically complex, highly regulated, time-consuming and expensive endeavour that required a globally attractive legal system to ensure the competitiveness of the pharmaceutical sector and internal market for medicines in Europe.

The 2004 revision of the general pharmaceutical legislation envisioned four main, high-level objectives:

1. **Ensure quality, safety and efficacy of medicinal products**. This means a robust authorisation system, surveillance and supervision are in place along the entire medicinal product lifecycle, including post-authorisation monitoring and pharmacovigilance procedures.
2. **Ensure access to medicines**. Health protection can only be effective if patients have equitable access to medicinal products as early as possible after authorisation.
3. **Ensure competitive functioning of the EU internal market.** Competition across medicine developers is expected to bring ever more innovative and effective medicines to meet the needs of patients in all Member States. This objective also considers a system where medicines that are no longer under patent protection (off-patent medicines) can be available in generic as well as the original branded forms so that there is a price competition benefitting national health systems.
4. **Ensure attractiveness in the global context.** Medicine development is a global endeavour, and it is important that Europe has a legislative framework that is globally attractive to medicine developers.

More specifically, these high-level objectives were expected to be achieved through a number of more specific objectives which were mutually reinforcing a more systemic view:

Accommodate innovation. This means that the legislative system is ready for the new scientific and technological developments that underpin innovative and effective products. Here innovation comprises not only new molecular entities but also adding value (follow-on innovation), repurposing existing medicines and developing biosimilar products. In other words, the legislation presents no roadblocks to innovation, rather, it is flexible and adaptable enough to enable new advances in medicinal products in a competitive environment.

Reduce administrative burden, improve adaptability of regulatory environment. This specific objective responds directly to the need for all medicine developers (including generic manufacturers) to navigate the regulatory landscape with minimum administrative burden (cost and time) and, as noted above, accommodate new scientific and technological developments. Therefore, rationalisation and simplification of the system was foreseen as far as possible to improve the legislation's overall consistency and visibility, the transparency of procedures and decision-making.

Reduce disparities and duplication of efforts. Historically, European countries had differing rules and processes that added complexity and resulted in duplicated efforts. Harmonisation and standardisation were promoted to reduce duplication, improve certainty and transparency to allow a level playing field for medicine developers across European MSs and transparent information access to patients. With the EU enlargement processes, this element received a particular focus.

Facilitate free movement of medicinal products. According to the concept of the internal EU single market, products should be traded freely across the Union. This objective aims to facilitate free trade for medicinal products through greater harmonisation of processes.

Regarding the broader policy context, the United Nation's Sustainable Development Goals (SDGs) were established in 2015 to succeed the Millennium Development Goals, as a global development framework to achieve better and more sustainable future for all. Although coming after the EU general pharmaceutical legislation was enshrined, the SDGs, in particular SDG Goal 3 of ensuring good health and well-being at all ages, SDG Goal 9 of building a resilient industrial infrastructure to foster innovation, and SDG Goal 10 of reducing inequality within and among countries, are consistent with the objectives of the general pharmaceutical legislation.

Multiple, interdependent impact pathways mediated by inputs and actions were foreseen in a complex pharmaceutical sector and health system for the four main objectives. These were expected to eventually lead to a higher level of health protection across Europe. The four key impact pathways are described below.

Impact pathway 1: Higher standards for the quality, safety and efficacy of medicinal products

A number of **actions** foreseen in the 2004 revision of the legislation were expected to lead to the achievement of higher standards for safe, efficacious and quality medicines: Changed documentary requirements, including environmental risk assessment (ERA); Harmonised application of good manufacturing practice for active substances; Reinforced inspections and increased coordination by introducing new tools; and more frequent submission of periodic safety update reports, harmonised national pharmacovigilance systems and inspections.

These actions were collectively expected to lead to the immediate results (or **outputs**): Quality control exercised over the life cycle of medicinal products; Strengthened market surveillance and safety monitoring; Effective information available for patient protection; and Decisions based on harmonised criteria, standards and protocols. Longer term these outputs should lead to the **outcome** that an effective monitoring system be in place in the EU covering the full lifecycle of medicines, which would ultimately enable the availability of efficacious, safe and high-quality medicines (**impact)**.

In addition, additional actions foreseen to accommodate innovation such as adaptation of the definition of a medicinal product, changes in the composition of EMA scientific committees and their mandate to provide scientific advice were also expected to contribute to this impact dimension, through outputs such as updated frameworks and procedures to accommodate new innovations and more effective coordination of advice and scientific support available to medicine developers. These outputs would promote the outcome of increased level of authorisation of innovative medicinal products, contributing to the impact of improving availability of medicines with a high level of safety, efficacy and quality in the EU.

Impact pathway 2: Improved access to medicines

The **actions** foreseen in the legislation to accommodate new scientific and technological developments in medicinal products included firstly the adaptation of the definition of medicinal product in the legal text taking account of these developments. Secondly, the composition of the various EMA committees was to be modified to reflect the ever more complex need to provide scientific advice to medicine developers. Pooling scientific expertise from MSs to guarantee a higher level of public health protection was one of the key aims of the revision (European Commission, 2002a). The 2004 revisions also introduced extra data protection periods for new indications for old medicines (repurposing). These actions taken together were expected to lead to the following **outputs**: updated frameworks and procedures to accommodate innovative products and treatments as well as effective coordination and scientific support available to medicine developers. These outputs, along with a reduced regulatory burden achieved from streamlined and harmonised authorisation processes, were expected to lead to a positive **outcome** which is an increased number of innovative medicinal products being authorised. Ultimately, the legislators foresaw that with increased number of authorised innovative products (partly through accelerated assessment and conditional marketing authorisation), patient access to medicines would improve (**impact**). However, it should be noted that while authorisation may be the first step in driving access of innovative medicines to patients, the EU does not have authority to ensure marketing in the different countries. Market launch in a Member State is a decision of the marketing authorisation holder (MAH). Access to patients in MSs is also down to

pricing and reimbursement decisions at the national and regional level by health technology assessment (HTA) bodies and healthcare payers based on cost-effectiveness considerations.

Impact pathway 3: A more harmonised, smoother and competitive functioning of the single market.

It was recognised that Europe needed to do more to remove barriers and harmonise processes to ensure that the internal market for medicinal products functions effectively and is competitive, and that patients have access to both originator and generic medicines as soon as intellectual property rights and regulatory protection periods allow. Therefore, a number of **actions** were initiated in the 2004 revision of the legislation. Data protection periods varied across the Union and this element was updated and harmonised (standard 8+2 years of regulatory protection was introduced across the EU), and the so-called 'Bolar' provision was introduced for research purposes wherein generic medicine manufacturers could have earlier sight of the regulatory data dossier so that R&D could be initiated to facilitate launch of generic products as soon as the 8+2 regulatory protection lapsed (Day 1 launch) (CMS, 2007).

In terms of medicine authorisation, the scope of the centralised procedure (CP) was expanded and a new decentralised authorisation procedure (DP) was introduced to help optimise procedures to obtain national marketing authorisations. This meant expanding EMA's central role in medicine authorisation, and at the same time, reducing the potential for direct referral to the Committee for Medicinal Products for Human Use (CHMP). A co-ordination group for mutual recognition procedure (MRP) and DP (Coordination Group for Mutual Recognition and Decentralised Procedures – Human, CMDh) was established with an explicit mandate to help to reconcile disagreements between Member States.

The harmonisation of data protection, introduction of the 'Bolar' provision, expansion of the scope of the CP and introduction of the DP were expected to act synergistically, leading to an increased number of authorisations through the centralised procedure and to a decreased number of referrals from the MRP and DP to EMA (**outputs**). It was also expected that therefore a greater amount of resources would be re-allocated to EU level activities from Member States, creating efficiencies.

In addition, regulators were mandated to make more information available to the public about medicinal products, including assessment reports prepared by national competent authorities and EU public assessment reports produced by EMA, the summary of product information and package leaflets (action). The new information provisions were meant to enhance transparency (output).

In the longer term, all the outputs were expected to contribute to **outcomes** that represent improved efficiency such as full harmonisation of the rules governing authorisation, production, distribution and use of medicinal products, and more generally uniformisation of processes and reduction of existing market barriers. Indirectly, these outcomes could be expected to contribute to other impact dimensions, including improving access to medicines across Europe through enabling authorisation of a greater number of innovative medicinal products (Impact Pathway 2) and improving the attractiveness of the EU market in the global context by reducing the regulatory burden (Impact Pathway 4).

Impact pathway 4: Improved attractiveness in the global context

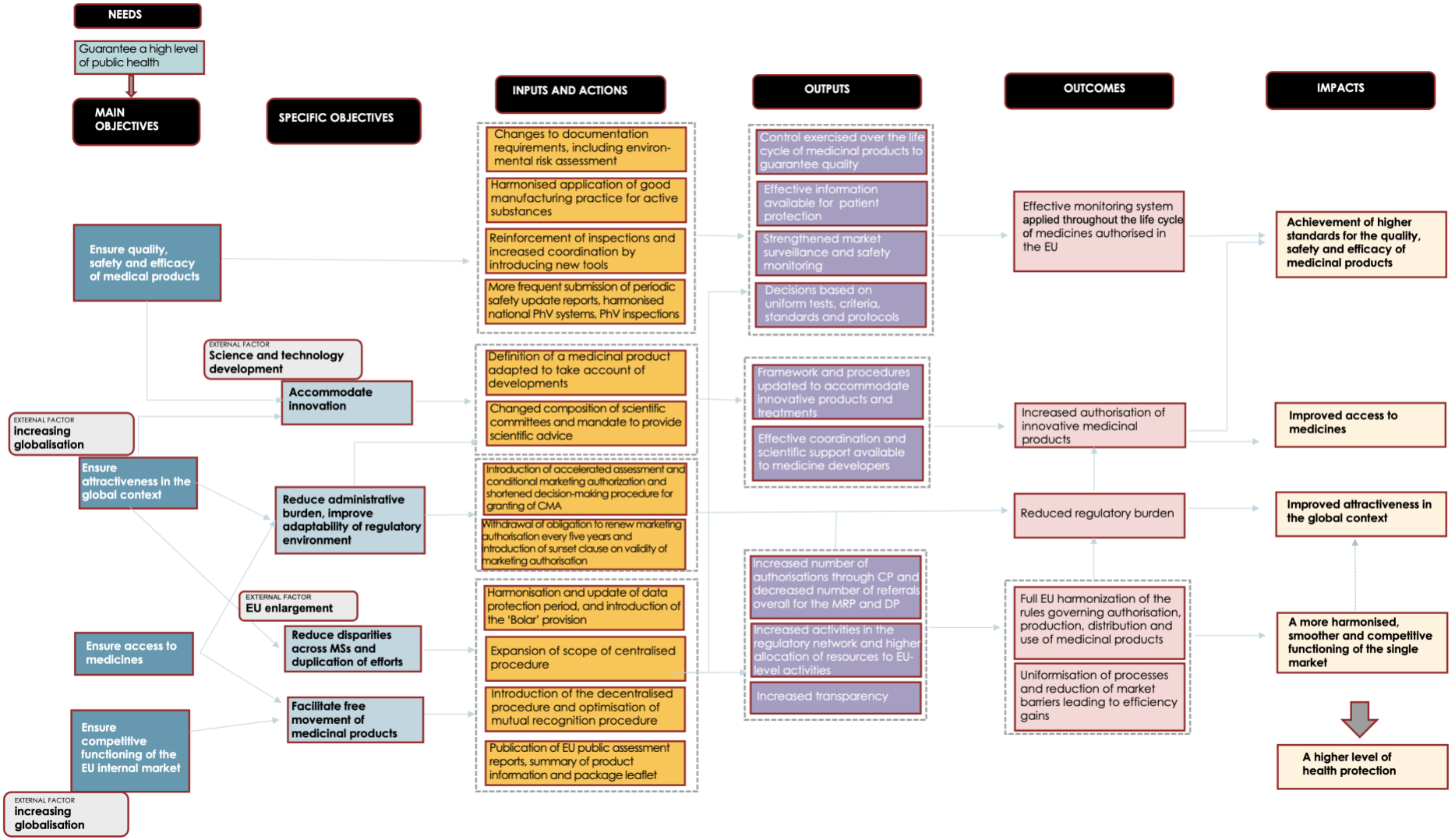
As discussed earlier, medicine development is a global endeavour and the revision put forward several **actions** to improve the EU's attractiveness for medicine developers. One such action is the withdrawal of the obligation to renew marketing authorisation every five years after the first renewal and introduction of a sunset clause on the validity of marketing authorisation. This action was intended to streamline processes and decrease the burden on marketing authorisation holders (MAHs). Another action undertaken as part of the revision was the introduction of accelerated assessment and the conditional marketing authorisation with a shortened decision-making procedure for the latter. This latter action was intended to facilitate faster decision-making processes to allow earlier access to innovative medicines for patients (European Commission, 2002b). Together, both actions were envisaged to reduce the regulatory burden for applicants (**outcome**), leading to the **impact** that overall attractiveness of Europe to medicine developers globally would be improved.

It should be noted that there are potential tensions or counterbalancing acts between objectives, i.e., reducing unnecessary burden while maintaining high regulatory standards; not hindering the

development of the pharmaceutical industry and achieving innovation while also ensuring access to medicines including generics and biosimilars. And therefore, several assumptions underpin the impact pathways as follows:

- Increased number of authorisations of innovative medicinal products leads to improved access to effective medicines in Member States;
- Accelerated assessment and conditional marketing authorisation lead to earlier access to effective medicines;
- Unnecessary administrative burden can be identified and reduced in such a way that it does not interfere with the robustness of authorisation processes;
- Health systems are in a position to administer innovative treatments, i.e., that the necessary skills, knowledge, infrastructure and resources are present, so the legislation contributes to public health protection;
- Innovative and generic product development continues to represent a commercial opportunity for the developer under the updated framework and procedures, i.e., that the market opportunity exceeds the cost and risk of medicine development, authorisation and maintaining the product on the market;
- External factors are aligned with the general pharmaceutical legislation in a way that these do not hinder the emergence of intended impacts.

Figure 1. Intervention logic of the 2004 revision of the general pharmaceutical legislation



2.2 Baseline: points of comparison

The Commission did not conduct a formal impact assessment for the revision of the general pharmaceutical legislation as it was not yet part of the standard procedure for adopting a legislative proposal. Therefore, the baseline has been reconstructed as far as possible based on available data, including by reference to the relevant explanatory memoranda for the changes and the audit of the procedures and operations of the European Agency for the Evaluation of Medicinal Products (CMS Cameron McKenna & Andersen Consulting, 2000; European Commission, 2002a, 2002b).

In Section 4, the changes and trends from 2005, when the revision was implemented, until the end of 2020 have been compared to the situation from 2000 to 2004 depending on availability of data (both qualitative and quantitative). In addition, the situation in the EU has been compared to other jurisdictions such as the US, Japan, Switzerland, Australia and Canada mainly in terms of the nature and burden of regulatory processes (including comparative legal analysis) as well as global competitiveness of the pharmaceutical sector. The key indicators used for the comparisons are indicated in the evaluation matrix (Annex II) and have been populated in the Analytical report. These cover parameters and areas such as new marketing authorisations (number, type of medicine and approval times), access and affordability (medicine price levels), clinical trials, medicine shortages in MSs (number and cause) and non-compliance with good manufacturing procedure (GMP).

Prior to the revision of the legislation (the baseline situation for the evaluation), the environment for pharmaceuticals was undergoing major changes with the enlargement of the EU and increasing globalisation of regulatory practices.

The pharmaceutical sector in the EU was not as competitive as that in the US in the 1990s. While scientific research was successfully organised in the US through smooth interaction between industry and public or private research organisations, fragmented EU MS policies did not result in the same level of interaction necessary for industry to successfully exploit the latest scientific results (Gambardella et al., 2000). Further, the fragmented nature of the European market for pharmaceuticals contributed to declining competitiveness, due to divergent public interventions and regulatory environment at national and regional levels (Gambardella et al., 2000).

European companies struggled to advance in innovative areas such as biotechnology and thus the European pharmaceutical sector was losing competitiveness. There were several reasons for this, including the lack of ability to organise innovation systems, higher labour intensity coupled with lower R&D value added activities, overall leading to a comparative disadvantage in selling their medicinal products in Europe (Gambardella et al., 2000). The restructuring of the health care system and consequently the demand for new pharmaceuticals in the USA benefited the technologically advanced, vertically specialised domestic pharmaceutical industry. European pharmaceutical companies tended to operate exclusively in their protected national markets which did not provide strong incentives to adopt innovation and globalised business strategies.

The continued enlargement of the European Union contributed to the need to establish an integrated environment for pharmaceuticals, as differences across the new Member States would amplify the problems of fragmentation and disparity. The legislative revisions thus had to be undertaken with enlargement in mind such that the adaptations to regulatory procedures would remain fit for purpose for expansion beyond the 15 EU Member States in 2002, and could accommodate scientific debates and take effective decisions with more countries involved (European Commission, 2002a). An integrated environment with harmonised systems and incentives at the EU level was regarded important to enhance EU-wide competition, improve efficiency of European companies, develop innovative medicinal products and reduce reliance on non-EU products to safeguard public health.

As noted above, the early 2000s was also a time of ever-increasing globalisation of regulatory practices and scientific and technical criteria for evaluating medicinal products across the world's three major pharmaceutical regions of the time – Europe, North America and Japan (European Commission, 2002a). This was a departure from the situation in 1995 when the new authorisation procedures (see below) were first introduced, and therefore the Commission had to consider the globalisation aspect in the 2004 revision to ensure international competitiveness of the EU regulatory system for medicines, as well as that the revised system was more modern, effective and lasting. By 2002, the Commission and Member States were actively involved, through their participation in

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), in the international discussions on technical and scientific requirements in the field of human medicinal products.

The European pharmaceutical system had two major routes to authorise medicines since 1995: the historic national authorisation route (and the related mutual recognition procedure, MRP) and a centralised route (CP) via the European Agency for the Evaluation of Medicinal Products, now named European Medicines Agency (EMA). The introduction of the centralised procedure allowed applicants to apply for marketing authorisation at EU level and place medicinal products on the market in all EU countries after regulatory assessment carried out by the EMA.

According to an evaluation of the EU authorisation processes of medicinal products conducted in 2000, both the CP and the MRP systems provided complementary benefits and contributed to a harmonised and efficient regulatory environment for medicinal products in Europe (CMS Cameron McKenna & Andersen Consulting, 2000). Nevertheless, the MRP system was seen as less successful in achieving harmonisation as some Concerned Member States continued to evaluate marketing authorisation applications, sometimes raising concerns that were unaligned with the recognition principle. It was pointed out that general supervisory and management support was lacking in this system and arbitration was not an efficient mechanism for companies. However, MRP was considered particularly flexible and met the commercial needs of smaller companies as they could get prompt access to major EU markets through the Reference Member State of their choice for first application.

The CP created conditions in which a single scientific evaluation of the highest standard could provide companies rapid access to markets for their innovative products. While this was the result of cooperation of EMA and Member State authorities, overall responsibility resided with EMA. It was however a challenge to maintain the breadth and depth of regulatory expertise at the EMA in the face of emerging technologies used by the pharmaceutical industry. While the EMA was effectively coordinating Member States' scientific expertise, it was suggested that specialist groupings with particular expertise needed to be created within the Committee for Proprietary Medicinal Products (CPMP), now known as the CHMP.

The early evaluation in 2000 attempted to compare cost-benefits of the two authorisation systems but it was not possible to measure cost efficiencies for applicants and the evaluation could not demonstrate economies of scale of the CPs with respect to MRPs. While the former was expected to suit the needs of larger companies, the latter would meet the needs of many smaller companies more efficiently. It suggested that while CPs helped harmonise standards and decision making, resource requirements actually increased through funding the EMA and involvement of national authorities in every assessment activity.

Regulatory data protection periods differed under the two approval systems and across national systems, which was believed to lead to differences in availability of innovative products on national markets and lowering pharmaceutical companies' willingness to invest in incremental research. Before the revision, MSs provided 6 or 10 years of data exclusivity, except for biotechnological and high-technology medicinal products which had 10 years of data protection (Adamini et al., 2009). Austria, Denmark, Greece, Finland, Ireland, Luxembourg, Portugal and Spain applied a data exclusivity period of 6 years.

It is important to remember that the organisation, provision and financing of healthcare is the responsibility of individual MSs in Europe. Consequently, MSs negotiate prices of medicines with suppliers (through payers) and make decisions on which medicines are reimbursed. This means that access to medicines can depend on a country's buying power. While this may reflect different historical social values and level of wealth across Europe, it hindered the creation of a unified European market with a lack of economies of scale and potential for competition, and even created inconsistencies, inefficient use of resources, and possibly uneven standard of medical care (Danzon, 1997).

3 HOW HAS THE SITUATION EVOLVED OVER TIME?

3.1 Implementation of the legislation

The negative trends observed in the EU life sciences sector in the 1990s regarding pharmaceutical R&D investment and competitiveness of the industry vis-à-vis global markets (Danzon, 1997) and the risk of exacerbation of a fragmented EU pharmaceutical regulatory system with further enlargement of the market with new Member States prompted the European Commission to devise a number of measures to reverse these trends. The 2004 revision of the legislation was delivered through two main legal instruments: the Directive 2001/83/EC and Regulation (EC) No 726/2004. These instruments have provided a comprehensive platform for the regulation of the lifecycle of medicinal products from development and authorisation to post-marketing monitoring and inspections of manufacturing and distribution. Even though several Member States were delayed with their national legislation to implement the changes to the Directive 2001/83/EC, the actual use of the new measures was not substantially delayed.

Some differences have been noted across MSs in the implementation of parts of the legislation. One area is the interpretation and implementation of the 'Bolar' provision by MSs. Individual MSs have transposed Directive 2004/27/EC into law at different times (mostly between 2005 and 2007), but the text adopted in each country can allow for different interpretations of the Provision (CMS, 2007). For example, in Spain the Provision can only be used for 'experimental' purposes and no commercialisation activity in preparation for market launch is allowed. On the other hand, in the Netherlands, generic manufacturers can prepare both regulatory procedures and production under the 'Bolar' exemption to enable Day 1 product launch. Another area of inconsistency across MSs is hospital exemption[3]. A recent study on how hospital exemption has been implemented in seven European countries showed great variations in the ways quality, safety and efficacy standards are implemented and controlled across EU MSs for ATMPs, which draws concern around potential impact on public health (Hills et al., 2020). Assessment of medicines containing or consisting of genetic-modified organisms (GMOs) is also complex and varies across the EU (e.g., assessment of their environmental safety) according to civil society organisations, industry and public authority stakeholders (public consultation and interviews). On occasion, this can lead to delays in clinical trials and authorisation of GMO-containing medicinal products according to industry stakeholders. The variations exist in the Contained Use versus Deliberate Release classification, risk classifications for the same GMOs (within Contained Use), and data requirements (content and format) (Beattie, 2021; Lambot et al., 2021).

3.2 Intellectual property and regulatory protection of pharmaceuticals in the EU

Protecting intellectual property (IP) is deemed necessary to drive innovation so that return on investment to research and development can be realised. There are multiple ways to incentivise and reward pharmaceutical innovation which is a long, expensive and risky process. Patent provides the basic protection and incentive to pursue innovation taking a novel concept to industrial application by excluding others from exploiting the invention for 20 years from filing date. Secondary patents are also known in pharmaceuticals and usually filed for improved variants of the basic product, new therapeutic indications, or new combinations. Since the commercialisation may take place late in the patent protection period, the EU introduced supplementary protection certificates (SPCs) in 1992 to offset part of the lost patent term. The combined IP protection period from marketing authorisation is limited to a maximum of 15 years.

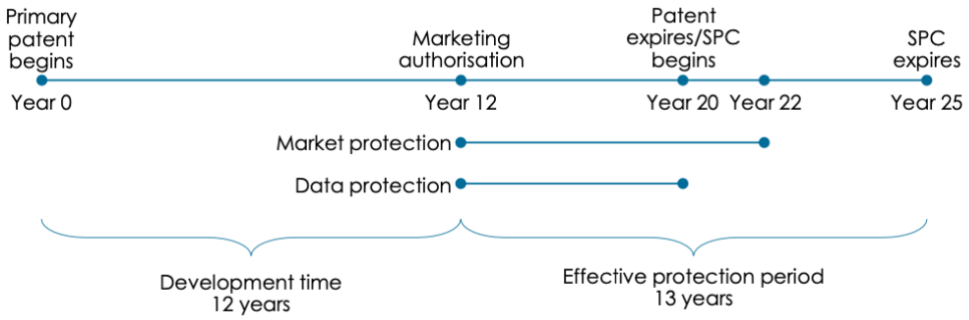
There is another protection type that is linked to the proprietary data that medicine developers collect on the quality, safety and efficacy of the product for the purpose of marketing authorisation. This data exclusivity or regulatory data protection period was standardised at 8 years in the revised pharmaceutical legislations. This means that a generic or biosimilar medicine developer can only refer to this data supporting their marketing authorisation after this period. There is also a market protection period that extends beyond the data protection period and in the EU it is an additional 2-year period when the generic version of the product cannot be placed on the market. The new

[3] A pathway that empowers EU Member States to permit the provision of an ATMP without a marketing authorisation under certain circumstances. It applies only to custom-made ATMPs used in a hospital setting for an individual patient. Such products may only be produced at the request of a physician and should only be used within the Member State where they are produced.

harmonised regulatory protection period has applied to new marketing authorisations for which applications were submitted on 30 October 2005 onwards.

There are additional incentives and rewards in the EU, including an additional year of market protection in case a new therapeutic indication for a protected product brings significant clinical benefit; 10-year of market exclusivity for orphan medicinal products, protecting those from competition from similar medicinal products; and an extension of 6 months of SPCs to reward paediatric investigations of medicinal products, and if the investigation concerns an orphan product, the orphan market exclusivity may be extended to 12 years.

Figure 2 Intellectual property and regulatory protection periods in the EU



Source: Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe (Copenhagen Economics, 2018)

The multiple possible protections can create a complex system and it is useful to focus on the expiry date of the last measure in place that protects the innovator medicinal product from generic competition in the EU markets. This may be SPC expiry or the regulatory protection expiry. A sample of 223 products in EU4 countries (France, Germany, Italy and Spain) with protection expiry between 2016-2024 shows that IP rights are the last to expire for about two thirds of the products in the basket (152), while regulatory protection is the 'last line of defence' for one third of the products (81). Similar results were obtained in a recent study (Copenhagen Economics, 2018) that found that 32-40% of products are protected by market protection. The same study found that pharmaceutical incentives and rewards in the EU are the most attractive when compared to Canada, China, India, Japan and the United States with regard to the basic regulatory protection periods (Table 1).

Table 1 Basic regulatory protection periods for pharmaceuticals globally

Country	Protection	Duration
Australia	New Chemical Entity + Market Protection	5 years
Canada	New Chemical Entity + Market Protection	6+2 years
Europe	New Chemical Entity + Market Protection	8+2+1 years
Switzerland	New Chemical Entity	10 years
USA	New Chemical Entity (small molecule)	5 years
USA	Biosimilar Application Approval Exclusivity (biologic)	4+8 years
Israel	Market Protection	6 or 6.5 years
China	New Chemical Entity	6 years
Korea	Post-Marketing Surveillance	Up to 6 years
Japan	New Chemical Entity	8 years

3.3 A regulatory framework to support innovation and access to medicines

Since the revisions in 2004, the European Commission has worked to balance competition and affordable access to medicine (Vancell, 2012). It has introduced or proposed legislative changes that are aimed at directing more innovation to areas of unmet need whilst placing greater obligations on product developers to ensure affordability and availability of products that benefit from innovation incentives. The regulatory framework for assessment and authorisation of medicines is underpinned by the aspiration to accelerate access. Meanwhile, efforts to improve cooperation and coordination between Member States in areas such as joint assessment and procurement have increased (de Jongh et al., 2021).

Antimicrobial resistance (AMR) is one specific area of unmet medical need where significant effort is made to stimulate innovation of new medicinal products. However, the pharmaceutical industry continues to experience headwind to address this challenge owing to scientific challenges and the limited financial incentive available to meet the cost of clinical development (Theuretzbacher et al., 2020).

The role of the EMA was reinforced through restructuring as well as introduction of new scientific committees and a mandate to provide scientific advice. The EMA's position has been further consolidated through its central coordinating role in the European medicines regulatory network within the new harmonised regulatory system. The mandatory scope of the centralised procedure for marketing authorisation has been gradually extended to new active substances that treat a number of conditions, including cancer, diabetes, neurodegenerative, viral and autoimmune diseases; medicines that are derived from biotechnology processes (e.g., based on genetic engineering, monoclonal antibodies), advanced-therapy products derived from blood, tissue and cells, and orphan medicinal products. There is also the opportunity for new active substances to use the centralised procedure which are outside the mandatory scope, including chemical, biological and radiopharmaceutical substances; and those that represent major scientific and technical innovation where authorisation would be of public interest.

As a result, the great majority of new, innovative medicines now pass through the centralised procedure and not the national authorisation procedures (MRP/DCP). Total central authorisations have more than doubled from a baseline of 30-40 products per year until 2004 to over 80 products by 2020, with new active substances making up about half of all central authorisations (ACC-1.1, Analytical report, 2022). When comparing central authorisations of new active substances in the EU with equivalent figures in the US (ACC-1.2, Analytical report, 2022), it shows annual authorisations in the two jurisdictions within a small margin between 2006-2016, however, with a new gap opening up in recent years, and US FDA now authorising more new molecular entities. The majority of new active substances were authorised first by the US FDA over the entire period 2001-2020 (53 to 75%), however the proportion of substances authorised less than 1 year earlier by the US FDA than EMA is increasing (from around 40% in 2001-2005 to 55% in 2016-2020; ACC-1.6, Analytical report, 2022).

It should be noted that the vast majority of product approvals continue to take place at the national level through MRP/DCP procedures (usually over 1000 products per year). However, currently, almost all medicinal products containing a new active substance are submitted through the centralised procedure. For instance, only 2 new active substances were approved via MRP/DCP from 2016 to 2020.[4] Since the introduction of DCP in 2005, the number of products seeking authorisation through the DCP has shown a marked increase with a parallel reduction in products following the MRP (ACC-1.3, Analytical report, 2022). Statistics from the CMDh and its precursor, the Mutual Recognition Facilitation Group (1995–2005), show a similar trend. In 2001, 423 MRPs were finalised rising to 954 in 2005. The DCP overtook the MRP in 2008 when 734 DCPs and 411 MRPs were finalised. In 2020, 856 DCPs were finalised covering 1793 products and 296 MRPs finalised covering 569 products. Note that the vast majority of the procedures concern generic medicines: 799 procedures in 2020 related to generics or other abridged applications.

[4] Heads of Medicines Agencies: Statistics (hma.eu)

3.4 Global position of the EU pharmaceutical industry

As regards external factors, it is important to note that in the past 20 years, the global market for medicines has rapidly grown. Between 2001 and 2020, global revenues tripled, reaching US$1.27 trillion (€1.2 trillion) in 2020 (Statista, 2021). The US is the largest market for pharmaceutical products, accounting for about 47% of the global market in 2021, followed by the EU market, the second largest, accounting for 19%. Revenue generated by pharmaceutical companies in the EU has increased over time and was approximately €200 billion in 2020 (IEC-10, Analytical report, 2022).

In the future, the global market for medicines is expected to continue to grow with a compound annual growth rate of up to 6% through to 2025 (Aitken et al., 2021), with a total market size of around US$1.6 trillion (€1.5 trillion, excluding COVID-19 vaccines). The market growth is driven by an increasing number of newly developed medicines, by emerging new markets and by rising prices in key markets (Aitken et al., 2021; Statista, 2021). A US$35 billion (€33 billion) increase of expenditure is forecast for Europe, mainly on biosimilars and generics. In particular, the immunology and oncology sectors are expected to grow up to 12% compound annual growth rate globally by 2025, with hundreds of new therapies and treatments being developed.

Increasing revenues and high profitability attract investment into developing new medicines, and in 2020, the total global spending on pharmaceutical R&D was US$198 billion (€188 billion) (Statista, 2021). The total number of products in active development globally in 2021 exceeded 6,000, up 68% over the 2016 level (IQVIA, 2022). Rich pipelines also translate into more medicine approvals and market launches – 84 new active substances were launched globally in 2021, doubling the number from five years before. 61% of these new launches were first-in-class[5], suggesting truly innovative pharmaceuticals emerging and not simply follow-on products (IQVIA, 2022).

The strongly growing global market has been an opportunity for the EU's world class pharmaceutical industry to evolve and capture a significant share of the increase. There has been an increase in total R&D expenditure, as captured by the EU R&D Scoreboard, doubling from around €20bn in 2000 to more than €40bn in 2019, albeit no significant change could be attributed to the implementation of the legislation (RI-8, Analytical report, 2022). The highest and most persistent growth in R&D investment in EU companies that operate in pharmaceuticals and biotechnology took place in 2011-2016. On the other hand, in the US, R&D investment remained almost stationary from 2003 until 2011 (close to €40 billion) and experienced significant growth in the period between 2014 and 2019 (reaching €74 billion).

While US firms show a lead in developing innovative medicines, the EU has become a global champion in manufacturing high-value medicinal products. Looking at the import/export levels and trends of medicinal products between 2000-2020, EU exports have increased five-fold and with €215bn worth of exports, medicinal products make up 10% of all exported EU goods in value. Imports have increased too, but at a lower rate, resulting in a massive €122bn trade surplus in this product category.

The value of EU28 imports as well as exports from and to non-EU countries has grown consistently between 2000 and 2020 for vaccines, finished pharmaceutical products and APIs (IEC-13.2, IEC-13.3 and IEC-13.4; Analytical report, 2022). Despite the fact that the EU imports large quantities of cheap generic medicines, vaccines and APIs from outside the EU, for example, from India and China, exports are greater than imports, except for APIs for which values are almost equal. The trade figures are the highest with the USA, exports significantly higher (€80bn in 2020) than imports (€20bn in 2020) and looking at a basket of six developed economies, the EU is by far the biggest provider of their imported medicines (Erixon & Guinea, 2020).

Looking at the profitability of the sector, according to public data, aggregated annual profits of pharmaceutical companies in the USA and Europe grew at annual growth rates of 6.6% and 3.1%, respectively during the 2003-2020 period (IEC-11, Analytical report, 2022). Nevertheless, the lower growth rates in Europe are correlated with a marked reduction in profits during 2016-2020. This

[5] Defined as a new and unique mechanism of action to treat a particular medical condition

period of decline in Europe was not observed in Switzerland or Japan, but Canadian companies reported negative profits during the same period.

3.4.1 Medicine prices

The affordability of medicines is an important factor for national health systems and patients, and it also has relevance to the profitability of the pharmaceutical industry. Medicine prices vary significantly between EU Member States. One study found an almost 11-fold difference between Interferone-beta prices in Germany (€1451) and Croatia (€133) (Zaprutko et al., 2017). For a sample of medicinal products, the same study showed that prices were the highest in Germany and cheapest in different EU countries but not in the poorest ones, such as Bulgaria or Romania. The medicines analysed were considered unaffordable for many EU citizens.

In the EU, average spending on pharmaceuticals as a percentage of health spending stood between 17–21% during the last 20 years (AFF-3, Analytical report, 2022). While this share was higher in 2003-2007, it has decreased slightly in the last 12 years. This figure is in line with the findings of a recent report by the IQVIA Institute highlighting that pharmaceutical spending has been growing more slowly than health spending in the recent period in most countries (Aitken et al., 2021).[6] The same report indicates that pharmaceutical spending is around €200bn in the EU, equal to roughly 1.5% of the EU's GDP.

Using net price data trends for all medicines sold in various markets between 2002-2020 (AFF-1.1, Analytical report, 2022), the average normalised price level (or cost to payers) is increasing steadily in all markets, with the EU being at an intermediate price level. Prices in Europe reached five times their 2002 level by 2020, and it is higher compared to Australia and Korea, similar to Japan, Canada or Switzerland, but significantly lower than the USA, where pharmaceutical prices increased rapidly since 2009. When focussing on medicinal products with total sales exceeding €10m, the trends remain similar but price level increases in Europe are relatively lower than comparators, with Korea being the only exception. When focussing on medicines with the highest unit prices, the trend remains similar, however when focussing on the relatively cheaper medicinal products, the price levels remain relatively constant (about 10% nominal increase on average) over the entire period between 2002-2020 (AFF-1.3 and AFF-1.4, Analytical report, 2022). This is below GDP growth of these countries with low price medicines' real prices declining further. We looked at the share of generics in the total sales value of pharmaceuticals and it remains at 15% with a rather modest growth over the period in Europe (AFF-4.2, Analytical report, 2022). The comparable value (i.e., share of generics in total sales) in the USA is 8% and in Korea 35%. When looking at the volumes of generics sales as a share of total medicine consumption, it was highest in the USA, reaching 70% of total consumption by 2020 from a baseline of 30% in 2002. The EU and most other comparators also experienced a rise in the share of generics, but at a lower growth rate. The share of generics in total consumption in the EU reached around 50% by 2020, up from approximately 25% in 2002. These results suggest that the price differential between branded and generic products is lower in Europe compared to the USA since generics account for a greater proportion of the total pharmaceutical sales value despite a lower proportion in total consumption. This is corroborated by an analysis of IQVIA MIDAS sales data, where the average generics price discount in the EU slowly rose from about 13% in 2002 to about 30% since 2011 (AFF-6, Analytical report, 2022). The evolution in the USA is, in comparison, much more dynamic. The discount on generics in the USA averaged 25% before 2012 and has risen to around 75% in 2020. Thus, a generic product in the USA on average costs only a quarter of its branded originator, compared to about 70% in the EU. The evolution of generics price discounts also seems more favourable in Canada and Japan compared to the EU, while Australia and Switzerland exhibit similar levels as the EU. On the other hand, generics entry has substantially decreased prices of branded medicines in the EU (up to around 60% lower by 2020) in contrast to countries like Australia, Japan, Canada, and particularly the USA, where branded products' prices *increase* after generic entry (AFF-6, Analytical report, 2022).

With regard to biosimilars, estimates suggest that global sales topped US$15 billion (€14 billion) in 2020, representing a compound annual growth rate of 56% since 2015 (McKinsey, 2021). The USA lags behind the EU in both biosimilar approvals and uptake, with the EU being the first to develop

[6] Spending inclusive of all products and locations where they can be delivered (retail, hospitals) and are reported after discounts and rebates received by payers

guidelines for the approval of biosimilars via an abbreviated registration process during 2005-2006 (GaBI, 2021).

Taking the quantitative analysis of how the situation evolved together with stakeholder feedback, it appears that the European pharmaceutical sector is in a stronger position than in the early 2000s, owing to a multitude of contextual factors (including the global environment) and cannot be solely attributed to the 2004 revision. The sector however did not manage to keep pace with changes in the USA both in terms of regulatory speed and flexibility and supporting innovation, developing novel medicines. It is important to point out that the two regions have markedly different systems for comparative cost-effectiveness assessment of medicines and ultimate pricing and reimbursement decisions. Moreover, as the data above shows the growth of the pharmaceutical market in the US is likely to be largely due to an increase in prices rather than increase in patient numbers per se. On the other hand, the EU has become a global hub in high-value manufacturing, and its pharmaceutical spending follows a more sustainable path and medicines are more affordable.

4 EVALUATION FINDINGS

4.1 To what extent was the intervention successful and why?

4.1.1 Effectiveness

This section of the evaluation report considers the effectiveness of the legislation, exploring the extent to which the actions implemented contributed to achieving its overarching and specific objectives and elaborating how the achieved results and impacts compare with the expected ones as per the intervention logic and impact pathways.

The targeted surveys provided an overview as to the extent to which stakeholders feel the legislation has been effective in terms of achieving its objectives. Stakeholder opinion across groups suggests that the legislation has been most effective regarding the objective of safeguarding public health and least effective in terms of ensuring access to medicines and addressing medicine shortages (see Figure 3).

There was good agreement across stakeholder groups on the most effective areas with only health services ranking "safeguarding public health" outside their top three and including "enabling progress in science, technology and digitisation" instead.

The areas related to access to medicines were areas where the legislation was deemed least effective by stakeholders. Enabling access to affordable medicines and enhancing security of supply of medicines were scored low by most stakeholder groups except for industry. Industry identified two different areas as the least effective. These were:

- Minimising inefficiencies and administrative burden of regulatory procedures;
- Improved global competitiveness of the EU pharmaceutical industry.

Overall, areas related to the other two main objectives: (1) ensure attractiveness in the global context and (2) ensure competitive functioning of the EU internal market were judged by survey respondents as effective to a moderate extent. Exceptions included industry which judged global competitiveness as one of the least effective areas (as discussed above) and civil society which scored "ensure a competitive EU market for medicines" very low on the effectiveness scale, with the view that legislation has not led to adequate competition in terms of either choice or prices.

Figure 3 Score of effectiveness of various areas of the current legislation

To what extent has the legislation been effective in contributing to the following objectives?	All stakeholders average score	Individual stakeholders average score					Agreement between stakeholders	Ranked Effectiveness
		Industry	Civil Society	Public Authorities	Academic	Health Services		
Safeguard public health	3.7	4.4	3.5	4.0	3.5	3.3	Low	most effective
Provide an attractive and robust authorisation system for medicines	3.8	3.9		3.8		3.8	High	most effective
Provide resources and expertise to ensure timely assessment and authorisation of medicines at all times	3.44	3.3		3.5			High	
Enable timely access to medicines for patients and health systems	2.9	3.2	2.8	3.1	2.7	2.8	High	
Enable access to affordable medicines for patients and health systems	2.4	3.0	2.0	2.3	2.1	2.7	Low	least effective
Minimise inefficiencies and administrative burden of regulatory procedures	2.8	2.3		3.0		3.1	Low	
Provide harmonised measures for an improved functioning of the internal market for medicines	2.9	2.7	2.60	3.5	2.8	2.8	Med	
Ensure quality of medicines including through manufacturing rules and oversight of manufacturing and supply chain	3.9	4.4	3.7	4.2	3.9	3.5	Low	most effective
Enhance the security of supply of medicines and address shortages	2.3	2.9	1.80	2.4		2.0	Low	least effective
Provide clear and appropriate responsibilities to all actors throughout the lifecycle of medicines, including post-marketing obligations and oversight	3.6	3.6		3.7			High	
Ensure a competitive EU market for medicines	2.8	3.1	2.2	3.0			High	
Improve competitiveness of EU pharmaceutical industry on the global market	2.7	2.4		3.1			Low	
Facilitate generic/biosimilar product entry to markets	3.3	3.6	2.7	3.3	3.3	3.44	High	
Enable progress in science, technology and digitisation for the development of high quality, safe and effective medicines	3.2	3.0	3.0	3.2	3.1	3.6	High	
Accommodate innovation for the development of complex and combination medicinal products	3.0	2.9	2.7	3.2	2.9	3.3	High	
Accommodate innovation for medicine manufacturing	3.1	3.2		3.2	2.9		High	
Attract pharmaceutical developers from outside the EU	2.7	2.7					High	
Reduce the environmental footprint of medicines	2.5	3.1	2.2	2.3			Low	least effective

Source: Targeted stakeholder survey analysis

4.1.1.1 Ensure quality, safety and efficacy of medicinal products

There is consensus across all stakeholders from the different consultation methods that the **legislation has provided a good framework for safeguarding public health**, and it has been highly successful in addressing this objective. For example, the majority opinion in the targeted survey indicates that the legislation has been most effective in areas that fall under the objective of ensuring quality, safety and efficacy of medicinal products (see Figure 33) such as:

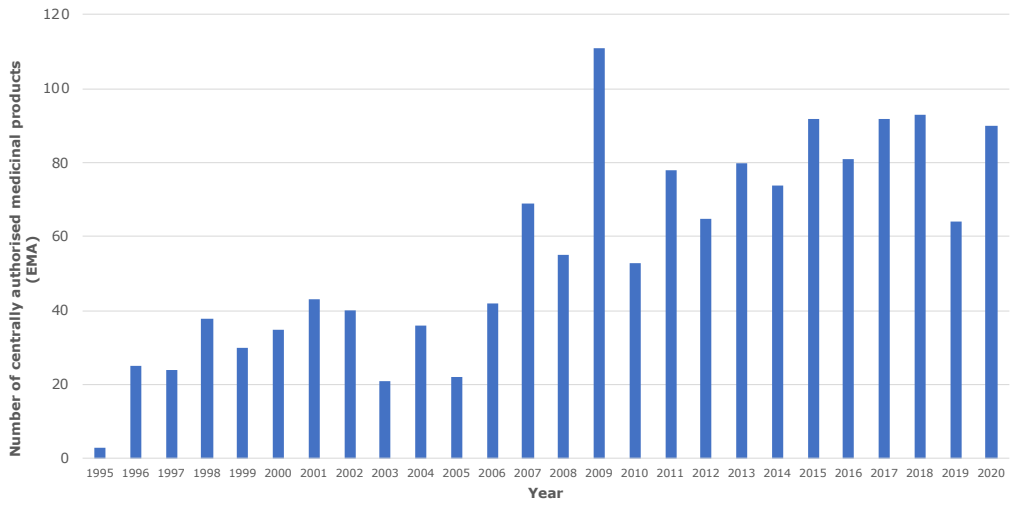
- Ensuring quality of medicines including through manufacturing rules and oversight of the manufacturing and supply chain;
- Provide an attractive and robust authorisation system for medicines;
- Provide resources and expertise to ensure timely assessment and authorisation of medicines at all times;
- Provide clear and appropriate responsibilities to all actors throughout the lifecycle of medicines.

The one area that may be linked to this objective and which scored low among stakeholders in the targeted survey and hence was deemed to be an area where the legislation had been least effective is the objective of reducing the environmental footprint of medicines.

According to interviewees across all stakeholder groups, one of the **major enablers for achieving this objective is the centralised procedure** (CP), which has allowed effective and robust authorisation of medicines at EU level. In general, stakeholders were highly positive in interviews about how the general pharmaceutical legislation has delivered a robust authorisation system for medicines. CP, decentralised procedure/mutual recognition procedure (DCP/MRP), pre-authorisation scientific advice and other services provided by EMA, accelerated assessment and streamlining of processes were cited as key achievements. These achievements have improved quality standards and have ensured safe and efficacious medicines are available to the EU population.

Figure 4 presents a time-series analysis of the total number of medicinal products that were granted a marketing authorisation under the EU centralised procedure per year (1995-2020). It underlines the feedback from our consultation on the effectiveness of the changes implemented in 2005, with a clear increase in the use of the centralised procedure over time, with the annual number of authorisations more than doubling on average. However, this may also be linked to the expansion of the scope of the centralised procedure.

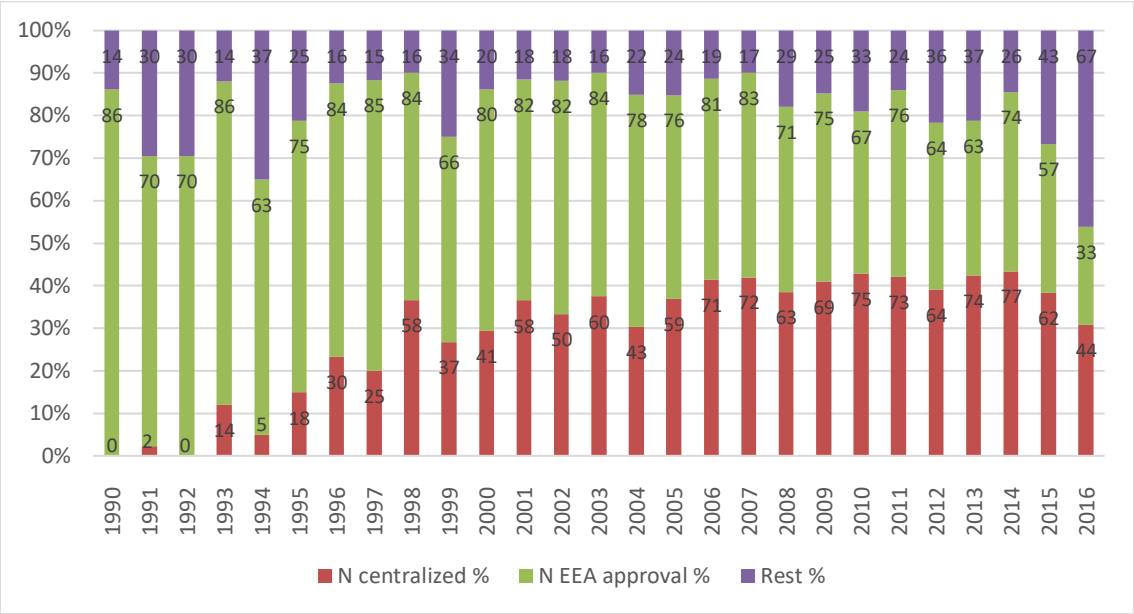
Figure 4 Number of medicinal products authorised through the EU centralised procedure (annual, 1995-2020)



Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA

Kyle (2019) reported the approval outcomes for new chemical entities (NCEs) that were introduced somewhere in the world from 1990 through to mid-2016. Figure 5 shows the share of NCEs that used the EMA's centralised procedure and the share that were launched somewhere in the EEA (N EEA approval), both relative to the number of NCEs first launched in each year. It is worth noting that since 2005 consistently a higher share of NCEs that were launched in the EEA used the centralised procedure compared to the previous years. This data supports the conclusion that the centralised procedure is the preferred route for authorisation of NCEs.

Figure 5 New chemical entities (NCEs) that were introduced somewhere in the world from 1990 through mid-2016



Source: Source: Kyle (2019), using data from IQVIA-MIDAS and EMA

Civil society and health services actors highlighted in interviews that there has been a significant improvement in the EMA's engagement, involvement and consultation with different stakeholders (including patients) and the scientific advice it provides, which has benefited patient safety. Better quality and safety of product manufacturing enabled by the 2004 changes to the legislation were also commented on by several stakeholders in interviews. This has been exemplified by EMA's role in coordinating regulatory action to reduce the risk of nitrosamine impurities in medicines described in the short case study box below.

The EudraGMDP database, which is the Community database on manufacturing, import and wholesale-distribution authorisations, and good manufacturing (GMP) and good-distribution-practice (GDP) certificates, shows that the number of third country registered API sites has almost doubled every year since 2019 (MI-1; Analytical report, 2022). By 2021, there were 6209 API sites registered in third countries (with links to companies with a main site registered in the EU). On the other hand, the number of API sites registered in the EU has seen a steady growth since 2013, although it almost doubled in 2021 when there were 1269 registered API sites (MI-2, Analytical report, 2022).

Regulatory action on nitrosamine impurities

Nitrosamines are a group of chemical substances that are classified as probable human carcinogens. In 2018, regulators were alerted to high level of nitrosamine impurities, N-nitrosodimethylamine (NDMA), in blood pressure medicines called 'sartans' that were produced by one API manufacturer. The discovery of this, triggered the EC to mandate the EMA to launch a review into all sartan medicines to assess the impact on the benefit-risk of these medicines to patients, which was later extended to other categories of medicines including ranitidine medicines. Based on the conclusions of the review, EMA set a temporary limit for nitrosamine impurities in medicines within a transition period of two years. Consequently, sartans and ranitidine medicines that were found to contain unacceptable levels of NDMA were subsequently suspended (European Medicines Agency, 2019).

In parallel, an EU-wide review in 2019 was launched to understand the presence of nitrosamines in all human medicines and to investigate the risks of nitrosamines coming through manufacturing into medicines. The review was published in 2020 and identified several root causes leading to the presence of nitrosamines in medicines based on which several recommendations were made to reduce the risk of nitrosamine impurities in medicines (European Medicines Agency, 2020a). An implementation plan was agreed in 2021 outlining how the European medicines regulatory network will work to implement the recommendations for all medicines authorised in the EU (European Medicines Agency, 2020b). Proposed steps range from providing guidance to reduce nitrosamines impurities to penalties for MAHs and other stakeholders if the quality of medicines is not ensured. However, this poses challenges for some API manufacturers in complying with the new requirements, which could lead to medicines shortages. To mitigate the risk of critical medicines being recalled if they do not meet the limit, the EMA has established a centralised benefit-risk assessment where higher limits may be accepted in order that these medicines continue to be available to patients. The case of nitrosamine impurities in medicines demonstrates the effectiveness of the EU regulatory framework to rapidly respond and adapt to new safety issues for medicines and thus ensure patient safety.

The stakeholder consultations also highlighted some areas for improvement, for instance, around the assessment of microbiome products, GMOs and environmental risk as well as better accommodation of bedside and decentralised manufacturing in the legislation or related guidance.

With regard to microbiome products, the European medicines agencies regulatory network strategy to 2025 confirms that there is a need for appropriate regulatory pathways for microbiome products (HMA & European Medicines Agency, 2020). There is no international harmonisation for microbiome products either (Cordaillat-Simmons et al., 2020) and there is a need to consider new regulatory approaches according to interviewed academic stakeholders.

Stakeholders' concerns regarding GMO requirements related to the safety of medicines are mirrored in the Commission's study on new genomic technologies (European Commission, 2021). Stakeholders were of the view that the GMO legislation needs to be updated to reflect changes in scientific understanding of GMOs and aligned with requirements under the general pharmaceutical legislation. For example, no environmental or biosafety risks are associated with non-replicating viral vectors or GM human cells, as these do not duplicate and cannot survive in the environment, and hence environmental safety requirements should be adapted accordingly.

Across the different stakeholder consultations, civil society organisations, public authorities and academics in particular highlighted the need for strengthening environmental risk assessment (ERA) requirements and more generally the environmental sustainability aspects in the legislation. Some of the stakeholders suggested exploring a more explicit role for ERAs in benefit-risk analyses during the assessment process, or even in pharmacovigilance (Technopolis, 2022a). In interviews, there were varied opinions on how well the legislation has performed in addressing pharmacovigilance. There was difference of opinion between and within the different stakeholder groups on this aspect. For instance, some stakeholders (from the public authorities, civil society, healthcare professionals and industry) felt that pharmacovigilance has substantially enabled maintenance of safety and quality of medicines. On the other hand, several stakeholders (healthcare professionals, industry) stated

that the new pharmacovigilance requirements have considerably increased the resource burden with little added value. However, they did not provide examples or data to further elaborate their view.

Interviews with stakeholders also highlighted issues with bedside and decentralised manufacturing. Concerns were expressed that these medicines may be excluded from the scope of the legislation falling under the category of magistral preparations (Pharmacy exemption) where there is less regulatory oversight, thus jeopardising quality and safety of these medicines (Technopolis, 2022b).

Another aspect highlighted in the public consultation and interviews by individual academics and NCAs was the potential need for further improvements to efficacy assessments as exemplified by the case of oncology medicines as described in the short case study box below.

Efficacy of approved oncology medicines

Davis et al. (2017) reported that of the 48 cancer medicines recommended for approval by the EMA between 2009 and 2013 for 68 indications, most (37 indications) entered the market without evidence of benefit on survival or quality of life.[7] A minimum of 3.3 years after market entry, there was still no conclusive evidence that these medicines either extended or improved life, and when survival gains were observed over existing treatment options or placebo, they were often marginal (Davis et al., 2017). Similar observations have been made regarding cancer therapeutics that received accelerated approval from the FDA by December 2020, with post-approval trials showing negative results for 10 cancer medicines across 18 indications (Gyawali et al., 2021). Thus, there is a view that the benefit of many new cancer treatments is not proportionate to their prices (Schnog et al., 2021). A study from 2021 shows that launch prices and post-launch price changes of patented anticancer medicines do not correlate with their clinical benefit (Vokinger et al., 2021). In such a situation, it may become difficult for payers to justify spending large share of their budgets on medicines with accelerated approval that cannot clearly demonstrate proven benefit on patient-centred outcomes (e.g., quality of life and survival). This concern, namely that innovative medicines may not always provide patient benefit commensurate with their costs, was also raised in the stakeholder consultations (public consultation and interviews) by a small number of national competent authorities, payers and academics (latter providing the particular example of cancer medicines).

Clinical trial design (lack of patient-reported outcomes, use of surrogate endpoints and single-arm randomised controlled trials, underrepresentation of minorities and older patients in trial populations), bias in data publication (to show greater clinical effects, non-publication or delayed publication of negative studies) and limited post-approval data for medicines that have been approved through expedited pathways are some of the factors that may lead to medicines with limited clinical benefit being approved (Gyawali et al., 2021).

4.1.1.2 Ensure attractiveness in the global context

The 2004 revision of the legislation was deemed an important step forward in ensuring a coherent and attractive regulatory system for developing pharmaceuticals in light of increased scientific and technological complexity of medicinal products and EU enlargement. Indeed, in the targeted survey, there was a high agreement among industry, public authority and health service stakeholders that the current legislation had provided an attractive and robust authorisation system for medicines (see Figure 3). In particular, the centralised procedure via the EMA allows developers to make the first steps to EU market access in an integrated fashion, which increases the EU's attractiveness as both market and location for pharmaceutical development and manufacturing. The EU has also been a global leader in setting up a process for licensing biosimilars, which encourages innovation and submitting market application in the EU compared to other jurisdictions according to industry interviewees in stakeholder consultations.

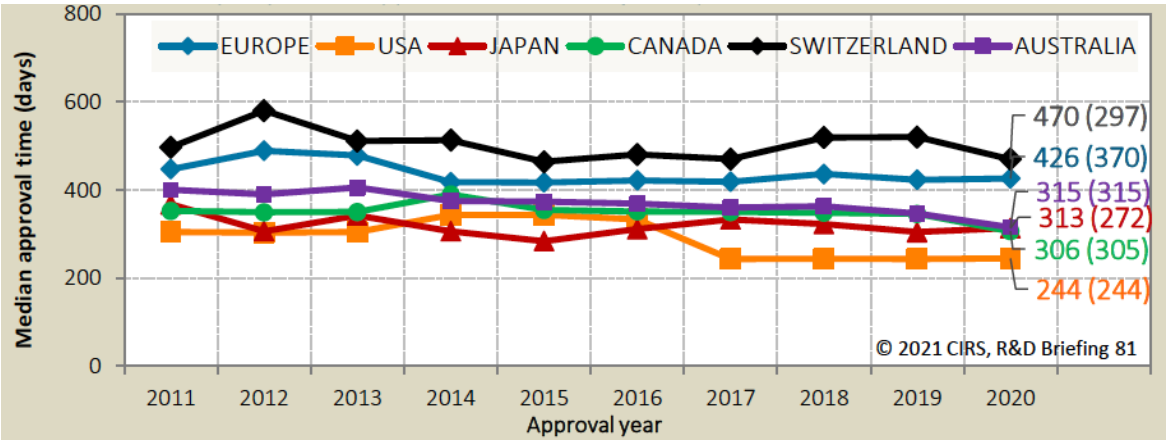
Yet, there are several factors influencing developers' strategies in relation to when and to which regulatory agencies they apply for marketing authorisation. The market size that the marketing authorisation (MA) gives access to is the biggest decision driver but there are other factors such as

[7] There was significant prolongation of survival in 24 of the 68 (35%) indications and improvement of quality of life in 7 (10%)

regulatory flexibilities or specific local epidemiological situations. The USA has the largest share of the global market for pharmaceuticals, more than twice the size of the EU market which has the second largest share of the global market (EFPIA, 2021). A 2021 comparison of six regulatory agencies (US, EU, Japan, Canada, Switzerland, Australia) by the Centre for Innovation in Regulatory Science (CIRS) (CIRS, 2021) found that new active substances (NAS) authorised by all agencies are first submitted to the FDA (USA) and on average only a few days later to the EU (with the EU being the second-choice jurisdiction). Submissions to the other agencies happened 63-150 days later on average compared to the USA. In addition, the proportion of FDA-authorised substances not authorised by EMA decreased (from approx. 40% in 2001-2005 to approx. 20% in 2011-15), with the exception of the latest period (2016-2020, 40%), which may be due to censoring issues of data publication (ACC-1.6, Analytical report, 2022).

The time needed for the assessment of the marketing authorisation application by the agencies is also an important factor for regulatory attractiveness. Figure 6 presents additional results from the CIRS annual analysis of NAS.[8] Data from 2011 to 2020 shows that the FDA had the shortest median approval time overall with the median approval time for the EU 182 days greater in 2020 than for the FDA. The study results suggest that shorter approval times may result from more new active substances going through expedited processes in the USA compared to the EU. Nonetheless, the shorter approval times may also contribute to greater attractiveness of the USA as a jurisdiction to submit application to before the EU.

Figure 6 New active substance median approval time for six regulatory authorities in 2011-2020



Source: Centre for Innovation in Regulatory Science annual analysis of new active substance approvals by the EMA, FDA, the Japan Pharmaceuticals and Medical Devices Agency (PMDA), Health Canada, Swissmedic and the Australian Therapeutic Goods Administration (TGA). Approval TMP by the agency. This time includes agency and company time. EMA approval time includes EC time. N1 = median approval time for products approved in 2020; (N2) = median time from submission to the end of scientific assessment for products approved in 2020

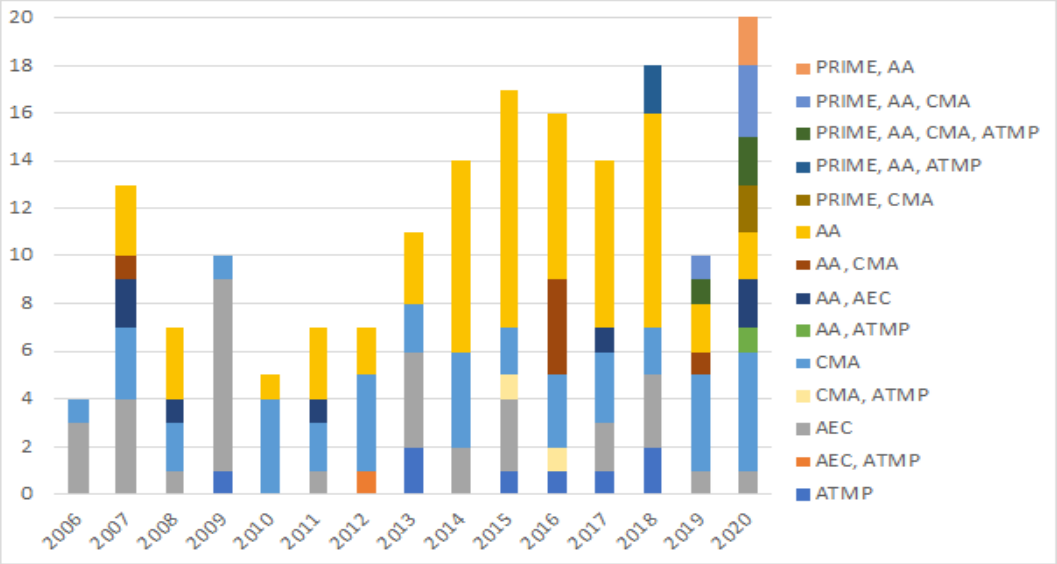
Several industry participants from stakeholder consultations confirmed that the FDA remains the preferred jurisdiction that developers want to file with, including those based in the EU. Reasons for these preferences can be differing data requirements for filing in the USA and EU, greater opportunity for direct interaction on scientific advice (mentioned by an SME) and need to interact with multiple EMA committees for ATMPs (up to five bodies for ATMPs targeting orphan indications, including the Scientific Advice Working Party). One SME mentioned that FDA is their preferred partner as the indication they are developing a product for fits more easily into the FDA's definition of unmet medical need (UMN).

Despite these reasons, the legislation has proven flexible enough to accommodate many developments and innovations in the pharmaceutical sector in the last two decades. There has been

[8] Approval time is calculated from the date of submission to the date of approval by the agency. This time includes agency and company time. EMA approval time includes the EU Commission time. N1 = median approval time for products approved in 2020; N2 = median time from submission to the end of scientific assessment for products approved in 2020.

a growth in the number of innovative medicines (Figure 7) including technologically innovative medicines (e.g. ATMPs) and those addressing UMN (e.g. through PRIME[9] and conditional marketing authorisation [CMA] routes). However, it was the view of several stakeholders that participated in our consultations that the system underpinned by the legislation has not been fully able to accommodate other emerging technological developments as readily, such as combination products/borderlines with medical devices or substances of human origin, digitalisation and new manufacturing methods. It was a common view in the consultations that one of the reasons for this problem is the lack of coherence in certain areas of the regulatory system, which can make it less attractive for developers, in particular for SMEs and companies that are less familiar with the EU system. For example, both public authorities and industry interviewees observed that medical devices, clinical trials and medicines are regulated by different regulations and competent authorities and have divergent requirements, making it difficult to coordinate approaches and navigate the system. As such, there are several areas for improving regulatory efficiency and coherence, in particular the complexities arising from the links between the general pharmaceutical legislation and other EU legislation. For example, the creation of different regulatory committees for assessing ATMPs, orphan and paediatric medicines should facilitate pooling of expertise and thus contribute to ensuring safety and efficacy of such products. However, it was the view of some industry stakeholders that it also created new layers of complexity, making it more difficult for marketing authorisation applicants to navigate the system and interact with each committee as they have different working timelines.

Figure 7 The number of innovative medicines authorised by EC, 2006-2020



ATMP = Advanced Therapy Medicinal Product; CMA = Conditional Marketing Authorisation; PRIME = Priority Medicine; AA = Accelerated Assessment granted; AEC = Authorisation under exceptional circumstances. Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA

4.1.1.3 Ensure access to medicines

Stakeholders (across different types and consultation methods) agree that there is room for improvement in terms of availability, access, affordability, and unmet medical needs (UMN) in the context of the legislation. Access to medicines is an area where the legislation is seen to have underperformed the most according to all stakeholder groups except for industry responses in the targeted survey. Access was viewed from three distinct angles by stakeholders:

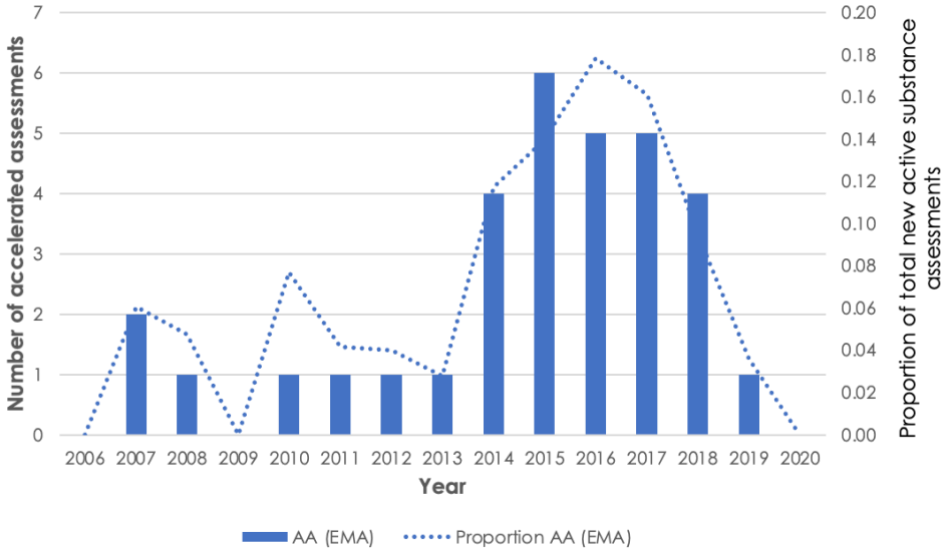
[9] PRIME is a voluntary scheme launched by the EMA to enhance support for the development of medicines that target an unmet medical need. Through PRIME, the Agency offers early and proactive support to medicine developers to optimise the generation of robust data on a medicine's benefits and risks, to optimise development plans and enable accelerated assessment of medicines applications.

- Evaluation and marketing authorisation of medicines
- Approval and reimbursement by HTA bodies and payers
- Medicine shortages

Of these aspects, the general pharmaceutical legislation is mainly responsible for authorisation, while reimbursement is completely out of its remit.

Medicine authorisation procedures, especially the centralised procedure, have allowed more new medicines to become available for the EU population (see Figure 4) – an outcome that was particularly emphasised by industry and public authorities in interviews. The EMA also gives the option of accelerated assessment to expedite authorisation of products of major interest for public health and therapeutic innovation and thus contribute to improving the speed of access to medicines. The number of accelerated assessments both in absolute terms and as a proportion of all assessments for new active substances have increased since 2013 (Figure 8).

Figure 8 Number and proportion of accelerated assessments by EMA

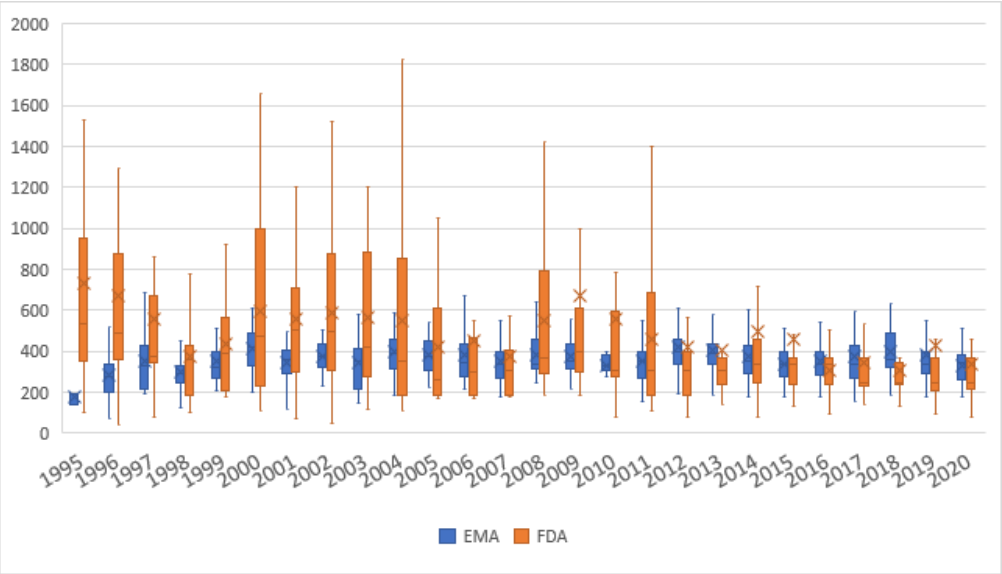


Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA

The 2004 revisions aimed for faster access to innovative products, so we have examined statistics on EMA assessment times. Figure 1 shows the trend in total assessment times by EMA (for centrally authorised medicinal products) and FDA in days (yearly, 1995-2020). The data show a notable improvement in EMA's average assessment times between 2005 (380 days) and 2010 (270 days), which then increased gradually over the next 10 years (340 days in 2020). This suggests the legislative revisions did improve timeliness, for a period before other factors (e.g. resourcing, more complex dossiers) resulted in a reversal. In comparing the EMA and FDA assessment times, EMA average assessment times are shorter than the FDA's for the whole period through to 2015, beyond which the situation has reversed with the FDA reviews taking 244 days on average compared with the EMA's 343.5 days. Whilst the difference is large, the indicators may not be fully comparable as the elements included in the assessment can vary.[10] The analysis also shows that the average FDA assessment times have been more variable than the average EMA times, over time.

[10] For example, the FDA time-data count from first application to approval even where initial applications may be refused and resubmitted several times, whereas the EMA counts time from the point of submission of the application to approval but only for the application that is ultimately approved.

Figure 9 Total assessment times of new active substances/new molecular entities authorised by EMA and FDA in days (yearly, 1995-2020)



Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA

Whilst the legislation has led to improvements in the authorisation of medicines, the system has also become more complex over the years according to the interviewees representing the industry. There are reported inefficiencies related to differing interpretation and implementation of the legislation and other relevant regulations and directives at the MS level (e.g. GMO, ATMP, BTC) which has led to delayed and unequal access across Member States. For example, under current procedures, generic medicines may require repetitive evaluation even where the active substance has been previously approved. Another area of inconsistency across MS as cited in interviews is hospital exemption[11]. A recent study on how hospital exemption has been implemented in seven European countries, showed great variations in how quality, safety and efficacy standards are implemented and controlled across EU MSs for ATMPs which draws concern around potential impact on public health (Hills et al., 2020).

While a marketing authorisation clears the first hurdle of getting safe and efficacious medicines to patients, it does not automatically imply availability for patients. HTA bodies and payers in MSs make reimbursement decisions based on their national assessments of cost-effectiveness of a given medicine. Even though the method of cost-effectiveness assessment can be similar across MSs, the outcomes of assessment may still differ substantially based on the local markets. This means that even if marketing authorisation processes are accelerated, the actual access to medicines is not uniform across MSs.

According to healthcare payers in the public consultations and interviews, HTA result shows that the clinical data available is often insufficient to quantify the benefit for patient care. They consider that such insufficient clinical data, e.g. 'immature' phase II data can sometimes be accepted for authorisation in accelerated/conditional approvals because of a perceived necessity for faster access for patients. However, without data showing verifiable clinical benefit and data transparency on which patient group would benefit the most, many products that enter the market are obliged to fulfil post-marketing conditions. These obligations are often fulfilled with delay, remain incomplete or the data submitted is insufficient to fill the knowledge gaps (Schnog et al., 2021). Therefore, evidence gaps

[11] A pathway that empowers EU Member States to permit the provision of an ATMP without a marketing authorisation under certain circumstances. It applies only to custom-made ATMPs used in a hospital setting for an individual patient. Such products may only be produced at the request of a physician and should only be used within the Member State where they are produced.

on cost-effectiveness may remain which has serious implications for payment and reimbursement decisions and thus ultimately access to medicines for patients.

The 2004 revisions expanded the scope of the centralised procedure and harmonised other procedures and rules to improve availability and access to medicines across the EU. The underlying assumption was that this would facilitate (and accelerate) the market placement of centrally authorised medicines in all EU countries as the central approval negates the need for the MAH to request authorisation in each MS individually. It would thus remove some of the costs and effort associated with these regulatory processes which had contributed to barrier to access. Note however that central authorisation itself does not oblige the MAH to enter all, or even a minimum number, of EU markets.

Crucially, access to medicines is not contingent only on medicine authorisation. Firstly, it requires a willingness by the MAH to place a product on a particular market, typically informed by the MAH's expectations about a positive return on investment in that market. Secondly, payers (health systems or insurers) need to agree to include the medicine in the package of reimbursed care. This may depend on an assessment of the expected (relative) cost-effectiveness of the medicine by the public authorities and the outcome of price negotiations between the MAH and health authorities. Such assessment procedures and outcomes may take months or even years and often strongly influence the actual time to launch a product on national markets.

A 2019 study found that the number of EEA countries in which a new chemical entity is launched has been steadily decreasing (Kyle, 2019). Various other studies have also shown that, even for products that have been approved through the EMA's centralised procedure, access[12] remains uneven across the EU. The evaluation of the EU Orphan Regulation showed that, in the first three years after marketing authorisation, EU authorised orphan medicinal products (OMPs) reached, on average, fewer than six EU-12 Member States[13] and that no medicine reached all Member States. A 2019 study in five European countries similarly found that in some countries less than a third of authorised OMPs were available to patients (Zamora et al., 2019). Also, for other centrally authorised medicines, such as oncology medicines, substantial differences have been reported in availability and time to entry (Bergmann et al., 2016; Ferrario, 2018).

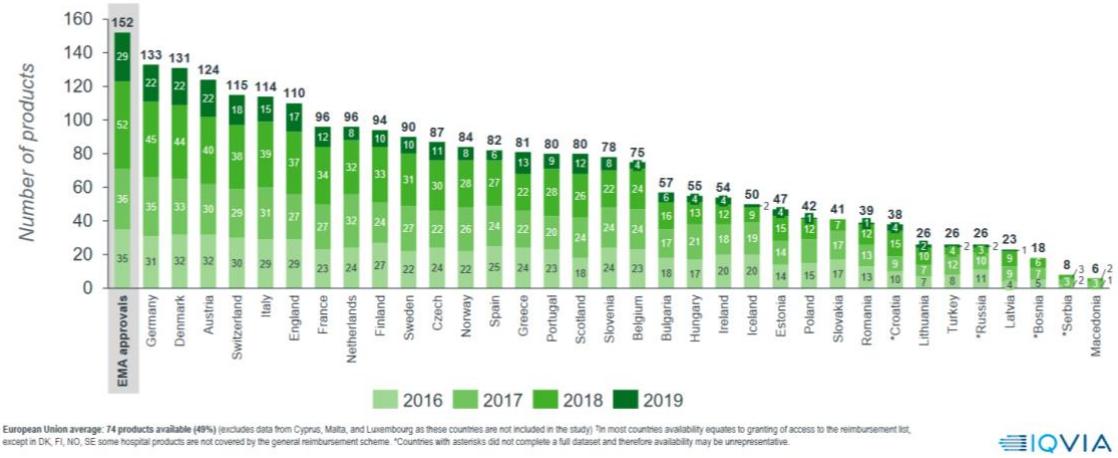
The fact that inequitable access is observed even for centrally authorised products points towards 'downstream' factors beyond the authorisation process that affect whether and when products are placed on specific markets. Such factors relate significantly to the characteristics of national markets. Smaller countries and poorer countries tend to see fewer product entries. To illustrate, data provided by EFPIA member associations and IQVIA showed that, whilst in Germany 133 out of 152 (88%) of all new medicines authorised between 2016 and 2019 were available to patients, small Member States such as the Baltic countries or countries with comparatively low price levels, like Romania, had fewer than 50 of these available (Newton et al., 2021). The time to patient access is also significantly longer for most of these latter countries, at approximately two years or more in Romania compared to four months in Germany. Similar observations were made across different subsets of medicines, including oncology medicines and orphan medicines.[14]

[12] Access is defined by fulfilment of the following criteria: 1) a medicine has been (conditionally or fully) approved for marketing in the country, 2) has been placed on the market by the MAH, and 3) is made available to patients as part of (partially) reimbursed care.

[13] To allow for the analysis to cover the full evaluation period from 2000 onwards, when the EU Orphan legislation was adopted, the analysis focused only on the 12 countries that were EU Member States in 2000.

[14] Oncology medicines and orphan medicines both fall within the mandatory scope of the centralised procedure and thus are authorised for marketing in all EU countries simultaneously.

Figure 10 Availability of EU authorised medicines (2016-2019) and their availability in MSs by the end of 2020



European Union average: 74 products available (49%) (excludes data from Cyprus, Malta, and Luxembourg as these countries are not included in the study) In most countries availability equates to granting of access to the reimbursement list, except in DK, FI, NO, SE some hospital products are not covered by the general reimbursement scheme. *Countries with asterisks did not complete a full dataset and therefore availability may be unrepresentative.

Source: EFPIA Patients W.A.I.T. Indicator 2020 Survey, IQVIA (2021)

Collectively, these studies suggest that expanded scope and use of the centralised procedure has not been an effective measure to improve access to innovative medicines in MSs and that more work needs to be done to ensure that a large majority of EU markets have access to authorised medicines.

4.1.1.4 Affordability

Affordability is an essential requirement of medicinal products so that patients can have access to treatment when they need it. In Europe, health systems provide Universal Health Coverage, however, patient co-payment rates for medicines remain high in some countries. The Pharmaceutical Strategy aims to ensure affordability of medicines for patients and health systems' financial and fiscal sustainability. Enabling access to affordable medicines is among the areas where the legislation has been less effective and more needs to be done according to all stakeholder groups in the targeted survey and public consultations. The rising costs of medicines and affordability (with their downstream impacts on access, health systems and public health) were key concerns for academics, healthcare professionals, public authorities and civil society stakeholders in the interviews – they were open to any measures that could conceivably address these issues going forward including incentives and new pricing models.

Pharmaceutical spending is the third biggest cost element in healthcare spending, roughly responsible for 1/6 of healthcare spending. According to OECD Health statistics, pharmaceutical spending (expenditure on prescription medicine and self-medication but not on medicines consumed in healthcare settings) remained stable over the last 20 years in EU28, at 17-21% (AFF-3; Analytical report, 2022). This is in line with the findings of a recent report by the IQVIA Institute that highlights that spending on pharmaceuticals has been growing more slowly than overall health spending in most countries, and below GDP growth (IQVIA Institute, 2021). It was noted that this share is lower in the Nordic countries (i.e. Norway, Sweden, Denmark 8-10%) and higher in Eastern European countries (i.e. Hungary, Bulgaria, Czech Republic 18-24%). To compare, IQVIA Institute reported values for Canada (10%), Brazil (13%), USA and Australia (14%), Japan (17%) and Korea (20%)(IQVIA Institute, 2021). Spending levels and trends also depend on therapeutic areas; spending on oncology products increased fastest between 2000-2020, due to increased need from the population and significant health burden, while spending on cardiovascular products decreased over the same period. Understanding spending in hospital settings is more complex (due to lack and inconsistency of availability data, different tax and supply chain costs, leading to nominal list prices only), however, there are indications that pharmaceutical spending in hospital settings has been rising faster than expenditure through the retail channel (OECD, 2020).[15]

[15] Annual average growth in retail and hospital pharmaceutical expenditure, in real terms, 2008-2018

The general pharmaceutical legislation does not directly address the affordability of medicines. However, Article 14(11) of Regulation (EC) 726/2004 lays down the principles of data exclusivity and market protection, which effectively prevents generic/biosimilar entry for 10 or 11 years (if additional authorisation granted for a new indication). This regulatory protection, together with patents, SPCs, and protection given to orphan and paediatric medicines delays market entry for follow-on products, generics and biosimilars, which are expected to lower price levels and increase affordability of medicines. Our analysis of top selling medicinal product sales data indicates (AFF-6; Analytical report, 2022) that branded product prices drop on average by one third of the price level prior to generic entry. This is the highest level among comparator countries, and similar to that in Australia and Korea. The discount of the corresponding generic products (compared to the price level of branded equivalent prior to generic entry) is even larger in the EU and steadily increased since 2007 from 50% to 65%, which means that the price of available generic products is only about one third of the price of their branded equivalent, before generics were available on the market.

As expected, the share of generics in total medicinal products sales revenue is modestly increasing in the EU (from 13% to 16%) between 2002-2020. It reaches the highest level in Korea (30%) and lowest in Japan and the USA (7%) by 2020 among the comparator countries. When looking at the share of generics volumes sold in the total volumes sold (in standard units), it grows from 25% in 2002 to 40% in 2020 in the EU. However, it grows even more in the USA from 30% to 70% in the same period, while in Japan the growth is more modest from 9% to 22%.

This shows that the EU is on a similar trend as other comparator markets and benefits from generic competition making prices of innovative medicines more affordable once the patent and/or regulatory protection periods expire. A sample of products of EU4 countries (France, Germany, Italy and Spain) with protection expiry between 2016-2024 shows that two thirds of the products are protected by intellectual property rights (patent and SPC) from generic competition, while one third of the products are protected by data exclusivity and market protection.

An example of the innovative biotechnology company Bluebird shows that innovative products command high prices that European markets are not always willing to pay. Bluebird's two gene-therapy candidates, namely Zynteglo and Skysona, were approved first by the EMA in 2019 and 2021, respectively, thanks to a favourable regulatory pathway but subsequent price negotiation did not lead to deals (Dunleavy, 2021; Taylor, 2017). Therefore, Bluebird decided to leave the European market altogether and submitted these products for review by the US FDA[16], in the hope that on the US market the company will be able to generate the expected high revenue to treat rare diseases.

Stakeholders interviewed (across different stakeholder types) agreed that the legislation has been beneficial for increasing competition in the pharmaceutical sector of the EU by facilitating generics and biosimilar entry in the market. This has been enabled by the Bolar exemption[17] which has allowed generics and biosimilars to be brought on the market more quickly. However, according to interviewees, the benefits from the Bolar exemption can vary across MSs because of differences in how the exemption is interpreted and implemented (CMS, 2007).

4.1.1.5 Medicine shortages

Medicine shortages present a major problem for the quality and continuity of patient care. A recent study (de Jongh et al., 2021) found that reported medicine shortages in the EU have increased over the last five to ten years and are placing a significant burden on health professionals and, ultimately are putting patients at risk of sub-optimal care and higher healthcare costs. The outcomes of the public consultations confirm the importance all stakeholders (and in particular civil society organisations and healthcare professionals) place on medicines shortages as a key issue impacting on access to medicines and ultimately public health. Health professionals stress that the current legislation has not been effective in addressing the issues of the medicine shortages as evidenced by rising shortage notifications. In the targeted survey, civil society, public authority and health service

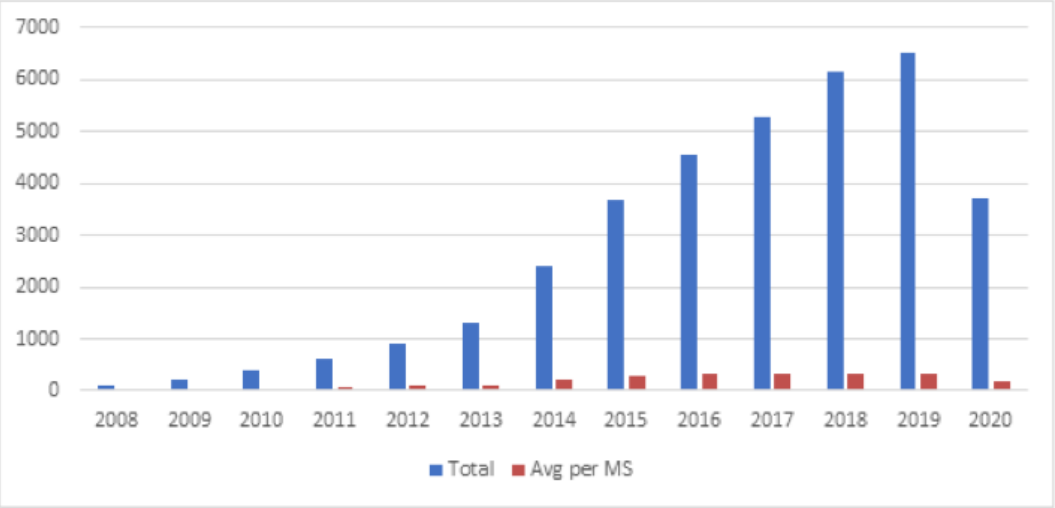
[16] FDA approved Zyntelgo in August 2022, and Skysona (by Accelerated Approval) in September 2022.

[17] The 'Bolar' provision allows certain experiments to be conducted on a patented pharmaceutical during the lifetime of the patent, to enable generic manufacturers to demonstrate e.g. bioequivalence prior to the expiry of a patent.

stakeholders considered the security of supply of medicines and medicine shortages to be an aspect that the legislation has been least effective in addressing.

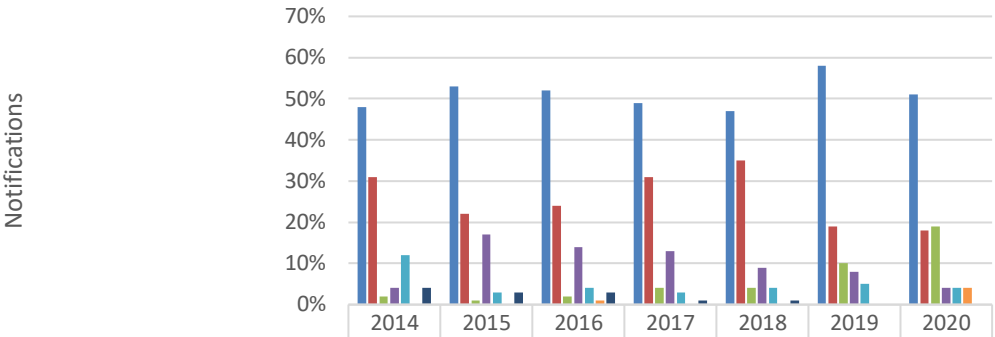
Figure 11 presents an overview of the total number of medicine shortages reported annually. It shows a strong increase in the numbers being notified over the last 10 years, suggesting increasing disruption for patients and health systems. However, there are other factors contributing to the increase, for example, there are more countries tracking and reporting shortages, and or doing so more effectively. Nevertheless, there is a clear increasing trend. Stakeholder feedback, collected both in this evaluation and in the previous study on medicine shortages, also suggests that shortages are indeed becoming more frequent. The implication is that, while the legislation has helped in creating more insight into the scale and the prevalence of medicine shortages (through introduction of shortage notification requirements), it has not sufficiently been able to address the reasons behind the shortages occurring nor has it enabled implementation of effective actions to alleviate their impact.

Figure 11 Total number of shortages reported across the EU



Source: Analysis of data from national shortage registries, Technopolis Group. The average number of countries reporting data on notifications from 2008-2010 is 2; from 2011-2013 is 7; and from 2014-2020 is 15.

Figure 12 Time trends in reported root causes of shortages (2014-2020)



	2014	2015	2016	2017	2018	2019	2020
Quality & Manufacturing issues	48%	53%	52%	49%	47%	58%	51%
Commercial reasons	31%	22%	24%	31%	35%	19%	18%
Unepected increased demand	2%	1%	2%	4%	4%	10%	19%
Distribution issues	4%	17%	14%	13%	9%	8%	4%
Regulatory issues	12%	3%	4%	3%	4%	5%	4%
Unpredicted major events or natural disasters	0%	0%	1%	0%	0%	0%	4%
Other issues	4%	3%	3%	1%	1%	0%	0%

Source: Analysis of data from national shortage registries, Technopolis Group.

Figure 12 presents an analysis of the root causes of medicine shortages, based on all shortages data from the period 2014-2020. It shows that quality and manufacturing issues dominate the statistics, reflecting unforeseen problems with the quality of ingredients or processes that lead to stoppages, recalls, etc.). The changes to the GMP/GDP guidelines and the more comprehensive scrutiny of manufactured quality / pharmacovigilance, are likely to have reinforced this trend. The dominance of 'quality and manufacturing' issues can also be seen as an example of the legislation having been successful in increasing the observance of manufacturing standards. Stakeholders, particularly industry and NCAs, report that generic medicines are particularly at risk of shortages, given the higher relative fragility of their supply chains. Supply chains for generics have become particularly vulnerable because procurement practices have driven down their prices to such an extent these products cannot be manufactured in the EU profitably and suppliers need to be consolidated, sometimes to one global supplier.

Figure 12 also shows that while manufacturing issues have become more important, commercial issues have decreased in importance, from around 30% of all causes in 2014 to 18% of the causes in 2020. Similarly, distribution issues have declined in importance over time. It is not clear whether this has to do with actual changes or the reporting differences. Taken together, the current pharmaceutical legislation is unlikely to reduce the actual root causes of medicine shortages.

4.1.1.6 Accommodating innovation

Developing new medicines is a capital intensive, high risk and potentially high gain business. Profits from new product sales and a supportive regulatory system with relevant incentives (e.g. intellectual property and regulatory protections) incentivise innovation. The interviews with stakeholders confirmed that the general pharmaceutical legislation has provided a regulatory system which has facilitated innovation across the product lifecycle. The centralised procedure, the creation of the EMA, the scientific advice procedures and overall harmonisation of quality and manufacturing rules were cited as some of the main enablers for accommodating innovation.

Most stakeholders confirmed that the legislation has proven flexible enough to accommodate innovation. However, some industry stakeholders observed that innovative manufacturing aspects are not adequately considered in accelerated approval pathways, which may cause bottlenecks and impact access. They also observed that overall accelerated approval pathways are not used as much in the EU as they are in the USA. According to the CIRS policy brief, 67% of new active pharmaceutical

ingredients were approved through expedited approval procedures in the US, versus 14% in the EU (CIRS, 2021).

Other stakeholders were of the opinion that the legislation has not been successful in increasing the EU's regulatory attractiveness in specific areas. These were related to a lack of adequate incentives for innovation by SMEs, academic/industry collaborations, innovation to address areas of unmet medical needs, generic and biosimilar innovation, and antimicrobial innovation. While out of scope of the general pharmaceutical legislation, there was also a broad consensus that health technology assessments (HTA) and pricing and reimbursement decisions are main drivers of innovation as these represent the return on investment into pharmaceutical R&D.

All stakeholder groups concurred that digitalisation and emerging science and technology developments have not been adequately integrated in the current regulatory system. Most stakeholders agreed that the legislation and related guidelines do not provide enough clarity for companies and national regulators when it comes to combination products (i.e. medical devices that also contain medicines), use of real-world evidence for clinical trials and medicinal products consisting of or containing GMOs. Similarly, a medical association cited radiopharmaceuticals as a key area where the legislation has not achieved a positive result in terms of facilitating innovation, citing lack of clarity in the regulatory framework for hospital preparations and lack of incentives for R&D in this area. The legislation has not managed to promote innovation in certain areas of unmet medical need such as AMR to the extent desired. Since the launch of the current regulation (2004), no new class of antimicrobials has been discovered globally (Lewis, 2020).

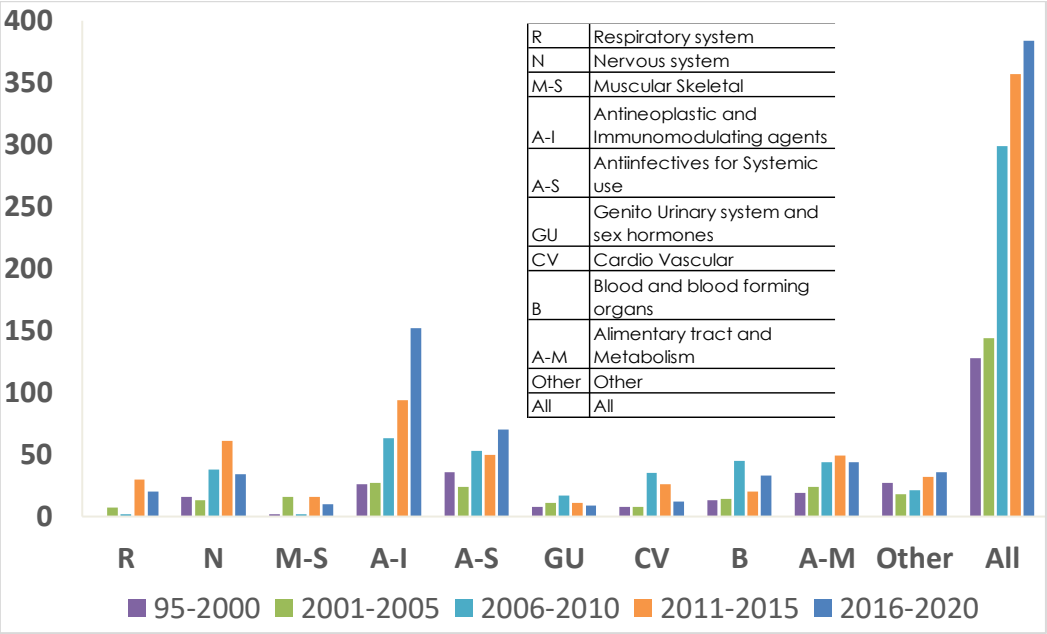
The 2004 revisions introduced several new procedures to encourage pharmaceutical companies to pursue development of innovative products relevant to unmet medical needs with a strong public health benefit, including the conditional marketing authorisation (CMA). The revisions also extended the scope of the standard centralised authorisation procedure and expanded the provision of scientific support / advice and strengthened the relevant EMA committees.

Another objective of the legislation was to attract R&D to the EU, thereby benefiting the EU economy. However, many other contextual factors affect such anchoring within the EU including R&D capacity, market size, availability of funding (public and private), tax system and incentives, etc. often at the national level. Across the EU, on average 1131 people per million population work in the pharmaceutical industry, similar to levels in the US and Japan, but lower than in Switzerland (IEC-7, Analytical report, 2022). As discussed in Chapter 3, the growth in the pharmaceutical sector in the EU as well as globally has led to an increase in total R&D expenditure, doubling since 2000 to more than €40bn in 2019, albeit no significant change can be attributed to the implementation of the legislation (RI-8, Analytical report, 2022). Nevertheless, R&D investment in the EU has remained significantly lower that than in the US (€74 billion in 2019).

The increase in R&D expenditure and introduction of revised procedures (e.g. PRIME, CMA) has translated to a growth in the numbers of innovative medicines approved with a consistent increase year-on-year from 2012 onwards (Figure 7).

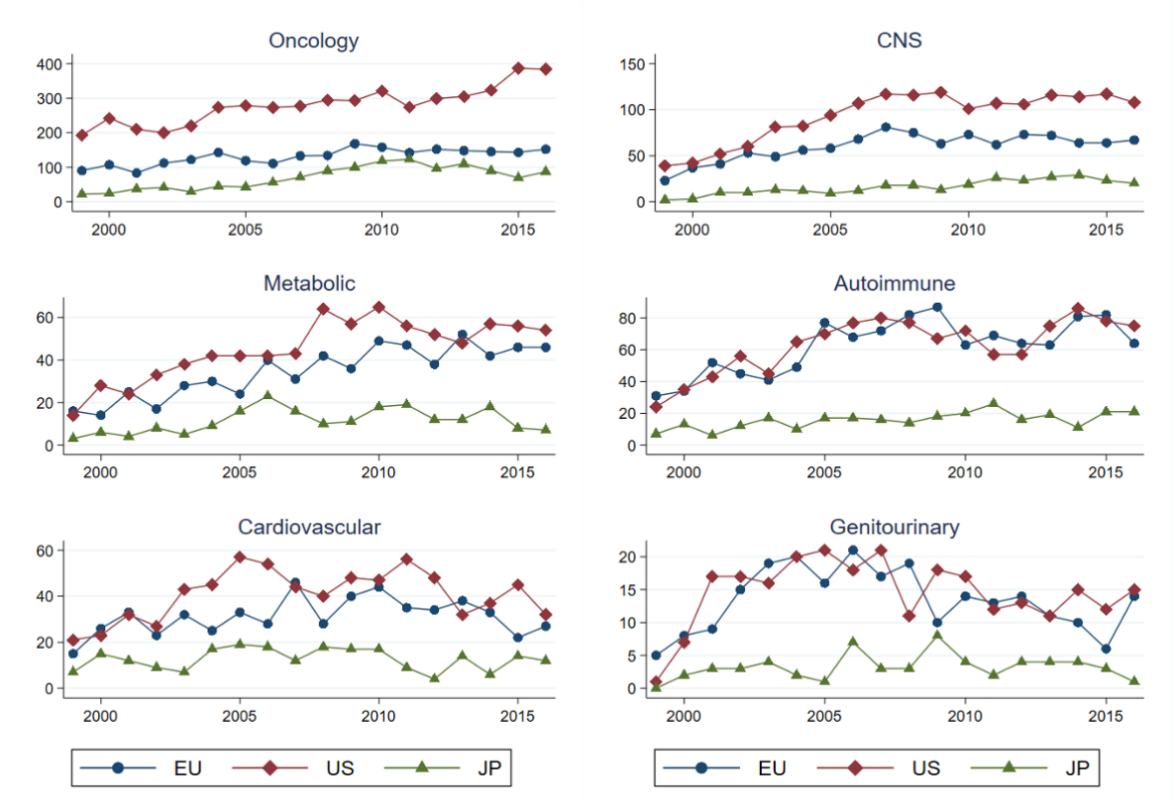
Figure 13 presents an analysis of the evolution in the number of medicinal products recommended for authorisation by the EMA in specific therapeutic classes. There has been an increase in the number of applications overall, likely due to the expansion in the scope of the centralised procedure, and this has been mirrored in large part across various therapeutic areas. The EMA statistics confirm this observation as most therapeutic areas show a sustained increase in the number of authorised medicines after 2005 following the expansion in scope. There has been a proportionately larger expansion (467%) in the number of authorisations of antineoplastics and immunomodulating agents, compared with the increase in the number of authorisations in other therapeutic areas, likely reflecting the expansion in investments in oncology and ATMPs.

Figure 13. Number of centrally authorised medicinal products by Anatomic / Therapeutic classification



R	Respiratory system
N	Nervous system
M-S	Muscular Skeletal
A-I	Antineoplastic and Immunomodulating agents
A-S	Antiinfectives for Systemic use
GU	Genito Urinary system and sex hormones
CV	Cardio Vascular
B	Blood and blood forming organs
A-M	Alimentary tract and Metabolism
Other	Other
All	All

Figure 14 Trends in the number of new candidate medicinal products (pipeline) per year, by therapeutic area in the EU, US and Japan



Source: Informa Pharmaproducts and FDA databases

Figure 14 shows that the number of new candidate medicinal products has increased steadily over time in all therapeutic areas, perhaps with the exception of genito-urinary medicines. The trends look broadly consistent across the three regions analysed (EU, US, Japan), which suggests EU market is functioning broadly in line with other regions internationally despite the different governance structures. However, there are no evident discontinuities in the EU trend data, around the timing of the implementation of the 2004 revisions, which suggests the legislation and the 2004 revisions have reinforced wider factors and have not boosted incentives substantially in the EU and nor have they hampered industry ambitions and competitiveness.

The 2004 revisions aimed to encourage firms to increase their development efforts with harmonisation of the period of regulatory protection across the whole of the EU (8+2+1 system). This was expected to lead to increased R&D investment, more clinical trials in the EU and an expansion in the medicines pipeline. These three expectations have been met to some extent at least (RI-8 and IEC-6, Analytical report, 2022); however, these effects cannot be attributed solely to the legislation or its revisions.

4.1.1.7 Competitiveness of EU pharmaceutical industry

The increasing complexity of the science and technology that feeds into pharmaceuticals has disrupted the traditional model of pharmaceutical companies that carried out all activities (or most) in the value chain: R&D, clinical development, manufacturing and marketing. The pharmaceutical industry is now much more divided in tasks and specialisation, with academic institutions conducting basic research and usually small businesses taking scientific discoveries into product development stages. In the clinical development phase, the costs sharply increase across the different phases of clinical trials, and usually this is the point when small companies either licence out their product, partner with or get acquired by large pharmaceutical companies. Large and well capitalised global companies are best in conducting and financing late-stage clinical trials, seeking regulatory approval and placing a product on the market. A high concentration of large pharma companies is observed among the market authorisation holders of innovative products (European Medicines Agency, 2021a), but this can hide the original innovator.

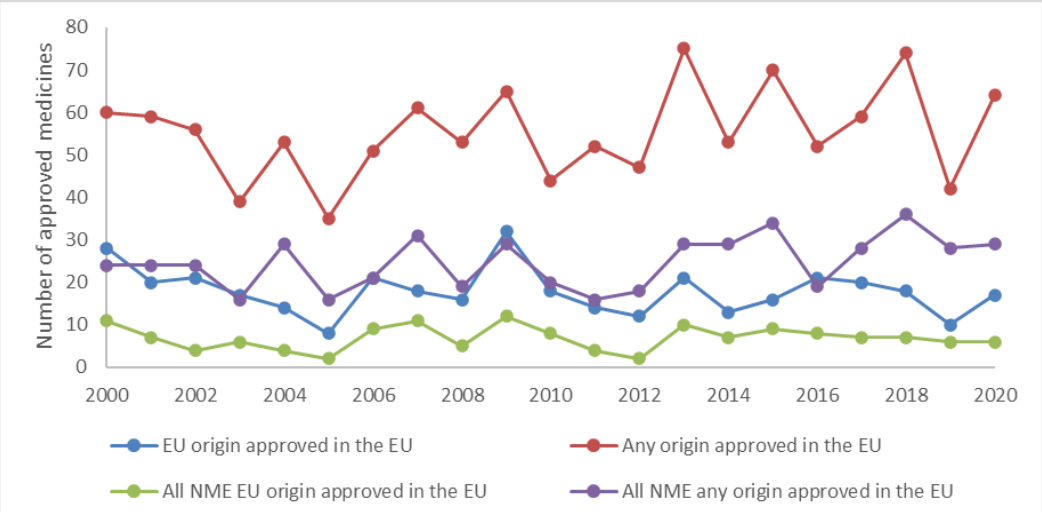
The greatest economic value from the pharmaceutical value chain stems from R&D, and thus this is a key factor to competitiveness. In the previous chapter we have outlined the EU's position in terms of pharmaceutical R&D. The EU has a strong second position globally, especially together with its close neighbours, the UK and Switzerland, that are part of the European biopharmaceutical innovation ecosystem through cross-country collaborations and movement of skilled professionals and capital. The EU biopharma industry's R&D expenditure has continuously grown in the last decades and only the US firms spend more in comparison. Between 2005 and 2019, employment in the EU pharmaceutical industry increased from 636,763 in 2005 to 795,000 (estimated), and employment in pharmaceutical R&D increased from 100,636 to 118,000 (estimated), according to EFPIA member associations[18] (EFPIA, 2021).

Figure 15 presents a time-series analysis of medicines approved in the EU that originated with developers based in the EU and those with developers based elsewhere in the world. It suggests the legislation and the 2004 revisions were largely benign in the impact on the relative attractiveness of the EU. We analysed the trends in the number of EU approved medicines ((i) novel, new molecular entities and (ii) all products including biosimilars and other generics) in order to understand whether the changed regulatory environment in the EU following the implementation of the 2004 revisions had provided an advantage to pharmaceutical companies based in the EU as compared with their competitors located elsewhere in the world and looking to sell into Europe. The analysis did not support our hypothesis that the 2004 revisions (expansion of the centralised procedure, greater harmonisation of processes and procedures, etc.) might confer a possible environmental advantage and boost to competitiveness for EU industry in comparison with its international competitors. However, the analysis (we ran the same analysis for all competing regions) suggests that any

[18] For pharmaceutical industry data includes Iceland (since 2017), Turkey (since 2011), Croatia and Lithuania (since 2010), Bulgaria, Estonia and Hungary (since 2009), Czech Republic (since 2008), Cyprus (since 2007), Latvia, Romania & Slovakia (since 2005), Malta, Poland and Slovenia (since 2004); For pharmaceutical R&D Data includes Iceland (since 2017), Greece & Lithuania (since 2013), Bulgaria and Turkey (since 2012), Poland (since 2010), Czech Republic, Estonia and Hungary (since 2009), Romania (since 2005) and Slovenia (since 2004) Croatia, Cyprus, Latvia, Malta, Serbia, Slovakia: data not available.

additional burden that may have been introduced by the 2004 revisions, such as ERAs and improved pharmacovigilance and manufacturing practices, did not disadvantage EU-based pharmaceutical companies when compared with their international competitors, either within the EU or when exporting to other regions outside the EU (our stakeholder consultations with industry suggest that overall the various revisions resulted in a net increase in total regulatory costs, estimated at 5-10% of total regulatory costs). The analysis found a small increase in the average number of annual approvals pre and post implementation for both the EU-origin medicines and medicines that originated with businesses located outside the EU. This does not rule out the possibility that the regulatory environment improved, to the benefit of both EU and non-EU industry.

Figure 15 EU-origin medicines and any-origin medicines approved in the EU, split by all medicinal products and new active substances only



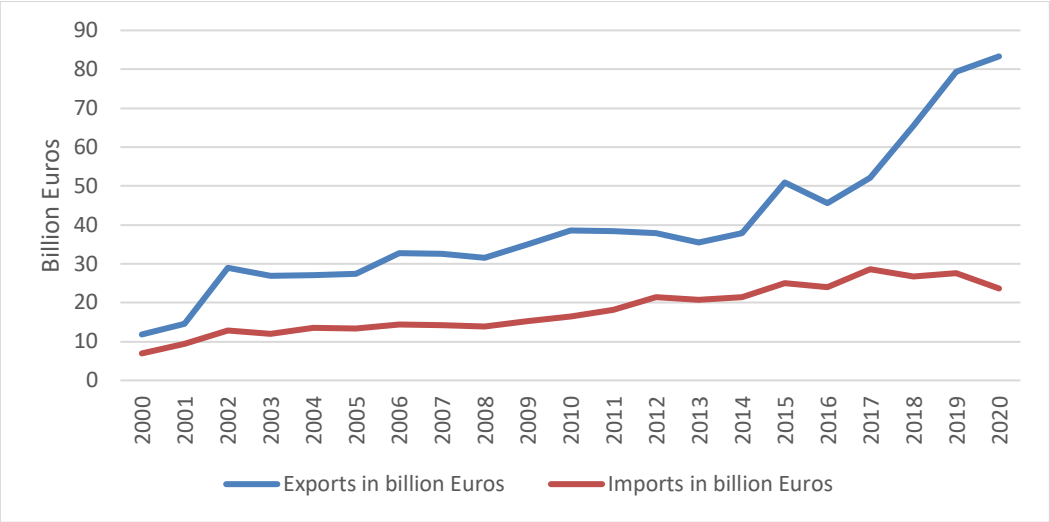
Source: Pharmaprojects, 2000-2020, Informa Pharma Intelligence analysis.

The landscape for pharmaceutical manufacturing has also changed in the last decades. Production of less complex products, such as small chemical molecules and traditional vaccines, has moved to the Asian continent, in particular to China and India (Progenerika, 2020) for off-patent medicinal products. In the EU, small and large companies have shifted production focus to more complex, biological products (e.g. products harvested from living cells), which require high-tech infrastructure, skilled work force and sophisticated processes. This has led to some companies offering contract manufacturing services as alternatives to in-house manufacturing and, as evidenced by export and import data, consolidated the EU as an important location for high-tech pharmaceutical manufacturers.

The EU has a large trade surplus in pharmaceutical products and is a leading exporter in developed markets. Between 2010 and 2019, there was a 78% increase in the value of EU27 exports of pharmaceutical products to other EU27 countries and third countries (Guinea & Espés, 2021) and while the overall figures are positive for the EU, there is no obvious effect of the 2004 revisions on the EU pharmaceutical industry's trade data. Other factors such as stable political and business environment, availability of skilled workers and existing infrastructure also play a role in EU's competitiveness, while high manufacturing standards and robust enforcement of good manufacturing practices increase the quality of EU-produced medicines, which contributes to investments in manufacturing.

We see no significant change in growth rates – for exports or imports – in the 3-5 years before or after the implementation of the 2004 revisions for the US (or with other regions). There are no evident discontinuities in the data. There have been no evident points of convergence or divergence. Figure 16 shows an example of one bilateral trading relationship between EU and the USA. We also looked at EU-Japan and EU-Switzerland, and found a similar absence of any obvious impact on EU trade flows or the competitiveness of EU industry.

Figure 16 EU medicines exports to and imports from the USA



Source: Eurostat

The EU's manufacturing capacity for exporting vaccines: COVID-19

The Comirnaty mRNA vaccine is an example of the EU's manufacturing capacity underpinning a globally leading role in exporting high-tech vaccines. BioNTech, the German biotechnology company that developed the technology behind Comirnarty, partnered up with Pfizer, a large pharmaceutical company headquartered in the USA with production facilities in the EU, to advance and scale-up human clinical testing and manufacturing capacity. By March 2021, less than three months after receiving conditional marketing authorisation from the EU (European Medicines Agency, 2022c), the BioNTech/Pfizer collaboration had already produced over 70 million vaccine doses in Germany and Belgium, placing the EU in the second place in manufacturing of COVID-19 mRNA vaccines, only behind the USA. In addition, British-Swedish company AstraZeneca, developer of the Vaxzevria vaccine, had produced over 10 million vaccines in the Netherlands and Belgium in the same period.

Through the export authorisation mechanism, the EU became the global leader in vaccines exports in 2021, supplying to the UK, Canada, Mexico, Japan, and many other countries. As of March 2022, the EU had nearly 40% of the global share of vaccine exports, as outlined below.

Total Number of vaccine doses exported by producing economy

Producing economy	Number of doses (million)	Share of world exports	Exports as share of total supply
European Union	2,276.2	39.7%	64.8%
China	1,869.1	32.6%	32.1%
USA	859.1	15.0%	58.4%
Republic of Korea	235.8	4.1%	91.1%
India	134.7	2.3%	5.7%
Russia	100.2	1.7%	35.8
South Africa	91.2	1.6%	87.0%
Japan	67.0	1.2%	99.8%
Other	105.9	1.8%	

Source: World Trade Organization. WTO-IMF Covid-19 Vaccine Trade Tracker[19].

[19] Last updated on 28 April 2022, with data for 31 March 2022 on WTO-IMF Covid-19 Vaccine Trade Tracker

4.1.1.8 Competitive functioning of the EU internal market

There are differing views among stakeholders as to what the internal EU market for pharmaceuticals is. In interviews, some stakeholders (e.g. civil society, healthcare professionals and public authorities) disputed the idea that there is a single EU market for medicines. Their view is that there are multiple national/regional markets in practice. It is also worth noting that markets can only be understood for individual therapeutic areas as there is no competition across therapeutic areas – as substitution is not possible. There is strong evidence and agreement across the various stakeholder groups that competition is suboptimal, for example from the targeted survey and interviews.

Nonetheless, many stakeholders agreed that the legislation has been beneficial for increasing competition in the pharmaceutical sector of the EU by facilitating generics and biosimilar entry in the market, particularly through the Bolar exemption. Generics entering the market are hindered by various factors including regulatory and intellectual property protection of the originator products as already discussed. Moreover, while these instruments define a clear date when generics can enter certain EU markets, generic entry in practice is somewhat delayed. This might be because of development and authorisation timelines (2-5 years for generics and 5-8 years for biosimilars; Mohammed, 2019) or lack of return on investment when developing a generic product. The total European biosimilar market has reached €8.8 billion in 2021 (Troein et al., 2021) while the generics market was valued at €67 billion for 2021 (Market Data Forecast, 2022). The market share and uptake of generics and the price reduction on generic entry has already been discussed in previous sections. The same aspects with regard to biosimilars are discussed in the case study below.

The EU has been an early adopter of biosimilars and delineated an authorisation pathway for biosimilars much before any other country. The biosimilar pathways are also a success according to industry and are seen as facilitating access of biosimilars to patients, thus increasing competition with the originator.

The EU's leading role on biosimilars

EMA first developed guidelines for the approval of biosimilars via an abbreviated registration process during 2005/2006, and since then EMA has developed many general and specific guidelines for biosimilars (GaBI, 2016). Based on these guidelines, 84 biosimilars have been authorised for use in the EU between 2006 and 2021 (GaBI, 2022). Biosimilars of biological reference medicinal products within the mandatory scope of the centralised procedure can be authorised only through the centralised procedure, whereas biosimilars of other biological reference medicinal products can be authorised through the other procedures. In practice, however, the vast majority of biosimilars are authorised via the centralised procedure.

IQVIA data show that the EU accounted for around 70% of the world's biosimilar authorisations in the 5-year period 2006-2010, and in 2016-2020 it still accounted for the largest share of authorisations (30%) (Troein et al., 2021). In comparison, the FDA only approved its first biosimilar in 2015, and has since granted 29 approvals for biosimilars with only 18 having been launched on the US market (GaBI, 2021). However, uptake (and access) of biosimilars is not uniform across EU MSs. On a per capita basis, central and eastern European markets lag western European countries (Troein et al., 2021). Uptake is affected by factors such as historic usage of protected brands, lack of clarity on the scientific foundation for interchangeability of biosimilars, national policies on interchangeability and lack of confidence in biosimilars among healthcare professionals and patients (Druedahl et al., 2022). There may be additional costs for biosimilar manufacturers to develop the same relationships with prescribers, key opinion leaders and patients as originators (to encourage prescribing) and for post-launch studies to assuage healthcare professionals' concerns as regards comparability of the biosimilar and originator (Mestre-Ferrandiz et al., 2016). These factors may also influence uptake of biosimilars.

The EC has actively promoted biosimilar uptake within the EU through its Project Group on Market Access and Uptake of Biosimilars. The group involves EU member states, EEA countries' representatives, as well as other stakeholders such as patient organisations, healthcare professionals and experts (Rémuzat et al., 2017). Member states have also provided targets and incentives for biosimilar uptake. For example, France has set a target of 80% biosimilar penetration by 2022 (Haustein et al., 2012). About a dozen countries in Europe including Germany and the UK offer incentives to prescribe biosimilars and countries such as France, Germany and Sweden have made arrangements to share benefits with patients (known as gainsharing).

Biosimilar entry creates competition, broadening patients' access to advanced treatments at more affordable prices and alleviating healthcare costs. In Germany, the waiting time for patients with rheumatoid arthritis to be treated with a biologic has been reduced from 7.4 years to 0.3 years after the introduction of biosimilars (Guntern, 2021). Biosimilars are typically cheaper by 20% compared to originator products (Chen et al., 2021). One study estimated the impact of biosimilar entry in terms of healthcare systems savings between 2007 and 2020 for eight EU countries (France, Germany, Italy, Poland, Romania, Spain, Sweden, and the UK), ranging from €11.8 billion to €33.4 billion (Haustein et al., 2012). Savings from biosimilars are smaller compared to generics at least in part because of the higher development and manufacturing costs as well as greater regulatory requirements to obtain marketing authorisation, which create barriers to market entry for competitors (Ferrario et al., 2020).

Ordinarily only one market authorisation is granted to an applicant for a specific medicinal product, however the applicant/MAH can obtain a duplicate authorisation at reduced cost for the same medicinal product where "*there are objective verifiable reasons relating to public health regarding the availability of medicinal products to healthcare professionals and/or patients, or co-marketing reasons*" (European Commission, 2019). MAHs have been making use of this exception to obtain a duplicate authorisation for the first generic product on the basis that its inaugural launch into the market can improve availability because it usually increases accessibility. This behaviour has implications for the biosimilar market (including anti-competitive effects) as national pricing, reimbursement and substitution rules are linked to the regulatory status of the medicinal product.

EMA statistics show that there has been a sustained increase in number of authorised medicines after 2005 in several therapeutic areas ranging from oncology and central nervous system medicinal products to those for autoimmune and metabolic disorders (Analytical report, 2022). These developments help to increase choice and competition for medicines within the EU.

4.1.1.9 Key contributing and hindering factors in achieving the intended objectives

The stakeholder consultations provided very little information on how the type of legislative act, i.e. a Directive, has impacted on achieving the intended objectives of the general pharmaceutical legislation. However, variations in the interpretation and implementation of the Directive when transposed by MSs were reported by stakeholders and is discussed in Chapter 3.

There is also a view among individual stakeholder organisations (industry associations, learned societies, SMEs) that the legislation and the incentives applied under it, predominantly incentivise development of traditional product types (e.g. small molecules) and new active substances and the innovation of radiopharmaceuticals, generics and cell-based therapies is not supported to the same degree. These types of medicinal products suffer from lack of coherence with and differing requirements under other regulations such as those for clinical trials and radiation safety (this point is further explained in the coherence section). The European Association of Nuclear Medicine in their statement of December 2021 identified challenges for radiopharmaceuticals within the Directive 2001/83/EC owing to uncertainties among MS authorities, producers and users in interpreting the Directive (EANM, 2021). This had led to increased heterogeneity in interpretation of the Directive and a negative impact on the availability of radiopharmaceuticals.

Moreover, in the public consultations, health professionals highlighted the inconsistencies within the legislation that have impacted on radiopharmaceuticals in particular. They pointed out that Article 6 paragraph 2 of Directive 2001/83/EC imposes the need for a marketing authorisation on "radionuclide precursor radiopharmaceuticals". In Article 1 instead of a definition for "radionuclide precursor radiopharmaceutical" a definition is given for the term radionuclide precursor. This has led to the unintended effect that all radionuclides regardless of the type of preparation they are used in (kit-type procedure or complex preparation) need a marketing authorisation to be distributed from a site that has the technical provisions for radionuclide production (accelerator, nuclear reactor etc.) to another site that is equipped for the radiosynthesis of the final radiopharmaceutical. Strict interpretation of the Directive therefore leads to the non-availability of radionuclides that are prepared by technically demanding infrastructure.

Along with the different routes for authorisation of new medicinal products, the harmonisation of incentives i.e. the 8+2+1 regulatory protection periods enables the legislation to meet its objectives even if EU trend data before and after 2004 indicates that the current system of incentives has not substantially brought more innovation compared to the previous system (Figure 9). The current incentives provide consistency and predictability to developers in terms of the marketing authorisation process and return on investment calculations, allowing easier 'go or no go' decisions with regard to pursuing R&D of a candidate medicinal product.

On the other hand, despite a large amount of R&D in Europe concentrated in universities and public research organisations, translation of academic research and innovation to marketable medicines is suboptimal. Many academics work on developing cell and gene therapies for cancers and certain genetic diseases. However, often the product cannot be brought to market as academics do not have the required regulatory knowledge and capacity, are not very experienced with product development and have limited production capacity (KWF, 2021). Moreover, guidelines and other regulatory standardisation are lacking because of the relative novelty of the field.

The interviews showed a consensus between public authorities, civil society organisations and academics that there is tension between the objectives of facilitating innovation and ensuring access to medicines. Data exclusivity and market protection incentives contribute to high prices according to these public sector stakeholders, which hinder access. While out of the sphere of influence of the legislation, HTA and reimbursement decisions have a major impact on population access to medicines in MSs.

Payers and civil society interviewees commented on the fact that data generated for obtaining authorisation are not useful for decision making by HTA bodies, payers and health professionals (i.e. safety and efficacy are often showed against placebo, and do not include the safety and effectiveness of the product compared to current standard treatment), and hence cannot sufficiently demonstrate the added therapeutic benefit during the reimbursement process for newly authorised medicines especially if they are expensive, leading potentially to delay of access.

Another key tension is between encouraging innovation focussed on addressing unmet medical needs or new antimicrobials and low return on investment (*AMR Review*, n.d.), which results in commercial entities not getting involved in R&D in these areas and impacts on the legislation's ability to safeguard public health in the EU.

4.1.2 Efficiency

4.1.2.1 Cost-benefit analysis

The socio-economic cost-benefit analysis follows the steps as set out in the Better Regulation Toolbox. The first step in assessing costs and benefits is to define the policy intervention to which they relate, and the hypothetical situation that would have occurred in absence of this intervention. We will use the term comparator situation in this analysis to describe the most likely situation in absence of the policy intervention.

The main measures of the policy intervention of the general pharmaceutical legislation have been set out in the terms of reference for the study.

For the comparator situation, it is noted that market trends in terms of medicine development and the pharmaceutical industry (innovation, mergers and acquisitions, etc.) would have taken place in and outside the EU. This means that in the assessment of impacts, such general (market) trends need, in as far as possible, to be separated from the 'pure' impact of the legislation. Thus, if the revision has stimulated innovation, that impact should be separated from the innovation caused by other factors, such as broader technological advances.

There is no unambiguous way to establish this comparator, as the revision touches on many aspects of development, production, distribution and use of medicines, some of which may have occurred (partly) also if the revisions would not have taken place. We therefore take the pre-2004 situation as the comparator situation and the analysis compares the situation before and after 2004 with respect to the legislation. However, as the pharmaceutical market has changed over time, both in terms of size and type of products, market changes may affect a comparison over time. Therefore,

general market trends are taken into account to compare the development in the EU with that in the USA, Japan and other relevant world markets.

Identifying the types of costs and benefits

The 2004 revisions were not accompanied by a comprehensive ex ante impact assessment, and as such the evaluation has sought to define the main types of direct and indirect costs and benefits, retrospectively. This has been done through our desk research and consultations. In the following table, we list the main types of costs or benefits for each of the main stakeholder groups, specifically:

- Industry relates to pharmaceutical producers based in the EU
- Trade relates to wholesale distributors active in the EU
- Regulatory bodies, separated into: EMA and NCAs
- Health system comprises healthcare providers, patients and their carers, and others in society

Table 2 Potential direct impacts

Actors	Type of cost / benefit	Direct impacts
Industry	Pre-marketing costs (e.g. R&D)	A mixture of cost savings (reflecting improved harmonisation and centralisation) and cost increases
	Post marketing costs	Cost increases associated with the strengthening of the EU-wide pharmacovigilance system
	Market access	Earlier access
	Market protection	Higher protection level
Wholesalers	Distribution costs	Harmonisation facilitating cross-border trade resulting in lower costs
EMA	Regulatory costs	Expansion in scope of activities creating a higher volume of work, resulting in higher operating costs
NCAs	Regulatory costs	Generally higher costs, some savings due to fewer authorisation procedures nationally
Health system	Quality of MPs	Measures generally result in higher quality / efficacy of products
	Availability of MPs	National health systems and patients have access to a larger number of innovative medicines
	Costs of MPs	Some products have longer market protection, which may result in higher prices
	Information on MPs	More and better information available, more informed decision making by reimbursement agencies and precribers
	Environmental impact of MPs	Improved transparency around the environmental risks of specific products / APIs, facilitating improved environmental management

We have collected primary data regarding costs and benefits through desk research, targeted survey and interviews. In addition to this, the results from analyses of secondary data (as presented in the Analytical report) has been used. These data, evidence and examples provided form the basis of our following cost-benefit assessment.

Measuring the costs and benefits

Given the length of time that has elapsed since the implementation of the 2004 revisions, most stakeholders were unable to provide quantitative estimates of the costs and benefits associated with those changes. Most could do no more than list the types of costs and benefits they had experienced, and the main drivers of those additional costs and benefits. Therefore, we have had to rely on quantitative estimates provided by a small number of organisations that had direct experience of the changes and some historical data. This limited number of observations was augmented by several studies and presentations, the number of data are scarce, and we have therefore come forward with large ranges for our estimates of the key impacts.

As described, the approach to identifying and measuring costs and benefits is by comparing the situation post 2004 revisions with the pre 2004 situation, taking into account general market developments when appropriate. The evidence for the size of costs and benefits has been gathered during this study from various sources: interviews, surveys and data analysis.

4.1.2.2 Stakeholder impact

The following sub-sections summarise the evidence on each of the potentially expected impacts of the 2004 revision, as to whether the expected impact (cost, benefit) has occurred and the magnitude of the impact.

Citizens and consumers

The 2004 revisions were intended to improve the quality and safety of medicines overall, through greater harmonisation of definitions and procedures between EU and MSs and among MSs and through a strengthened EU-wide pharmacovigilance system. The revisions also effectively increased the incentives for industry to develop novel medicines through the expansion in the scope of the centralised procedure and the harmonisation of the period of regulatory data protection.

In both cases, our consultations and desk research confirm a positive impact of the revisions on both the quality and safety of medicinal products available in EEA and the number of innovative medicines available to healthcare systems and patients. Our consultations found a generally positive view across all stakeholder groups that the 2004 revisions in general and the more comprehensive inspections and pharmacovigilance systems specifically had delivered a higher level of patient protection as compared with the earlier arrangements.

Table 3 Summary of estimated costs and benefits of the 2004 revisions of the general pharmaceutical legislations

Direct costs	**Citizens / Consumers**	**Citizens / Consumers**	**Businesses**	**Businesses**	**Administrations**	**Administrations**
	Quantitative	**Comment**	**Quantitative**	**Comment**	**Quantitative**	**Comment**
Direct Compliance costs (adjustment costs)	-	-	€250m	Additional investments in IT systems to cope with expanded data requirements on safety and manufacturing, estimated at 0.1-1% of sales. Using the 0.5% median value gives a gross figure of €750m for the EU industry overall. However, the new IT systems have provided wider benefits / productivity gains, so the attributable cost is assumed to be lower (1/3 of gross costs)	-	-
Direct compliance costs (adjustment costs)	-	-	€50m-€100m p.a., €750m-€1,500m in total	Higher costs due to data requirements for new and current marketing authorisations; additional costs for legal departments	-	-
Enforcement costs: (costs associated with activities linked to the implementation of an initiative such as monitoring, inspections and adjudication/ litigation)	-	-	-	-	EMA: €2.5m-€3.1m p.a., NCAs: €8m-€25m p.a.	Higher staff and evaluation costs for EMA; higher inspection costs for national competent authorities

Direct benefits	**Citizens / Consumers**	**Citizens / Consumers**	**Businesses**	**Businesses**	**Administrations**	**Administrations**
	Quantitative	**Comment**	**Quantitative**	**Comment**	**Quantitative**	**Comment**
Health Impacts	25-30 new innovative medicines, in total; producing 170,000-210,000 QALYs in total; which amounts to €4.8bn-€17.2bn in	The additional number of new products has been estimated based on a comparison between EMA and FDA	-	-	-	-

	monetised benefits, using WHO guidelines on valuing QALYs	authorisations over time; the QALYs are based on estimated average EU income and a median ICER				
Compliance costs: MAH savings	-	-	CP: €4.8m p.a., DCP: €36m p.a.	Cost savings due to the harmonisation and streamlining of procedures associated with the introduction of the DCP and the substantial reduction in the use of the mutual recognition procedure	-	-
Compliance costs: MAH savings	-	-	€23m p.a.	MA holders benefited from the switch to a single renewal of a MA 5 years after the original notice of authorisation, eliminating the need for further renewals at 5-yearly cycles, and removing the need for renewals by generics companies	-	-
Enforcement	-	-	-	-	€20m-€40m pa	Cost savings for national competent authorities due to streamlining / harmonisation of national authorisation procedures (switch to DCP away from MRP)

There is no good direct measure of medicine quality that one can link clearly to the legislation, however, statistics do show strong year-on-year growth in the numbers of GMP inspections in the five years following the implementation of the 2004 revisions (EudraGDMP database),[20] clearly reflecting the legislative decision to expand and harmonise the oversight of MA holders' manufacturing and supply chains as a means by which to ensure quality and consistency. These activities have continued – and have been strengthened further – over the ensuing 15 years, ensuring the quality of both manufacturing and distribution (European Medicines Agency, 2021b). The number of GMP inspections and certificates issued by EEA authorities was running at around 2,500 a year pre-COVID,[21] with this extensive programme of quality assurance work resulting in a small but highly variable number of non-compliance statements (i.e. identified quality problems) of 0.1-1% of inspections (1-24 non-compliance statements each year in the past 10 years).

There has been a similarly evident expansion in the numbers of safety reports submitted and recorded in the EudraVigilance database, again suggesting the regulatory system is working well. The time-series data published in the EudraVigilance annual report to the Parliament and Council show a clear change in the rate of growth in the numbers of individual case safety reports (ICSRs) being submitted and screened annually, following the 2004 revisions (European Medicines Agency, 2020c). Around 10% of the individual safety reports are judged to warrant an in-depth review by the EMA's signal management team or a Lead Member State (for nationally authorised products) for a possible adverse drug reaction (ADR) and around 20% of these assessments result in a referral to the Pharmacovigilance Risk Assessment Committee (PRAC). Around half of these referrals to PRAC result in an update of the product information for patients and healthcare professionals, thus providing updated guidance on the safe and effective use of the medicines. We have not reproduced the actual statistics here, as these potential safety issues can have many causes, and they do not provide a credible basis for directly measuring quality improvements attributable to the legislation.[22] Notwithstanding this important caveat, the 2004 revisions did however provide the legal basis for the improved monitoring, and the change in the number and trend of reported safety concerns is a good indication that the surveillance system was successfully enhanced. We were similarly unable to quantify the benefits of these quality enhancements to public health in the EU, but studies of more recent enhancements to the overall pharmacovigilance system show the process is identifying more potential risks and enabling these to be acted upon more quickly and decisively (Potts et al., 2020).[23]

The expansion in the scope of the centralised procedure and the extension of the period of regulatory data protection has contributed to an increase in the numbers of innovative medicines being authorised for use in Europe. As such, EU citizens have had access to a larger number of novel medicines than would have been the case without the 2004 revisions. The number of newly authorised medicines increased in the period following the introduction of the revisions, with the number of applications and authorisations almost doubling in the 10 years following, from around 35 in 2005 to around 70 in 2015 (European Medicines Agency, 2021a).[24] The same has happened in respect to innovation with the numbers of medicines containing new active substances (NAS) increasing from around 20 a year to around 30. This growth in medicines and NAS is partly a reflection of changes in the scope of the EMA's centralised procedure but it is also a reflection of wider trends, with increasing demand for new medicines globally and an expansion in R&D investment by pharmaceutical companies the world over (OCDE, 2019).[25]

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[20] The data derived from the EudraGDMP database, however, the EMA Annual Reports include a chapter on inspections and compliance that provides a more accessible analysis of activities over the current and two previous years. As a case in point, see page 59 of the 2007 Annual Report.

[21] The number of inspections – and physical visits in particular – was reduced substantially during the COVID-19 pandemic, with some potential lessons for streamlining and digitalisation going forward. See the results of an annual survey of inspections and audits.

[22] Better monitoring may mean revealing pre-existing issues to an extent and there can be many reasons for ADR which can include genuine scientific unknowns at the time of the original authorisation or time-limited manufacturing issues and even off-label uses.

[23] In the period 2012-2018, the EU's strengthened pharmacovigilance process resulted in over 26,000 potential signals being reviewed and 453 confirmed signals assessed by the PRAC. More than half of the PRAC recommendations have resulted in changes to medicine product information supporting safe and effective use of medicines, demonstrating that the EU signal management process reliably detects, assesses, and deals with safety issues and enables the risk of ADRs to be minimised.

[24] In 2021, EMA recommended 92 medicines for marketing authorisation. Of these, 54 had a new active substance which had never been authorised in the EU before.

[25] This report reviews the important role of medicines in health systems, describes recent trends in pharmaceutical expenditure and financing, and summarises the approaches used by OECD countries to determine coverage and pricing.

Given the widely differing types of novel medicines recommended for authorisation, from cancer to infectious diseases by way of cardiovascular medicines, and the impossibility of inferring which specific products have been brought to market that would otherwise have not been, we have had to make some broad approximations as regards an 'average' innovative medicine in order to estimate an average number of citizens (patients) that may benefit from access to these new treatments, and the likely health gain in terms of Quality Adjusted Life Years (QALYs).[26]

These estimates are set against the backdrop of a reducing EU health burden more generally: research confirms that age-standardised mortality rates have improved in all EU countries in the period since 2007 (Santos et al., 2020), albeit with significant variations in improvements across member states. There are also major differences in the burden / mortality across diseases, with heart conditions, strokes and various cancers dominating the top 25 conditions.[27] These long-term improvements have been attributed to improved education, better socio-economic conditions, stronger public health systems as well as advances in healthcare. The regulatory system will have been an important contributor too, driving innovation in new medicines as well as ensuring the safety and efficacy of the 900,000 medicines[28] recorded in the EMA database (as defined under Article 57).[29]

There is no simple means by which to estimate the numbers of additional new medicines authorised and launched on the market that are attributable to the 2004 revisions, however, there is a clear discontinuity in the EMA trend data with the 3-year averages declining at around 10% a year across the period 2001-2005 and then growing at around 20% a year from 2006-2009. The US FDA authorisation data exhibit a similar trend, but with a 3-year delay. Within the period, the EU changes from authorising 5-10 fewer products each year to authorising 5-10 more than the FDA. The trend data suggest the US regulatory system had adjusted by 2010 with the FDA once again authorising more innovative medicines annually than the EU. The two regions' 3-year averages mirrored one another through to 2016, after which there was a marked divergence in outputs between the regions with authorisations in the US growing strongly while the EU recorded a period of low or no growth in product authorisations. From this perspective, we have assumed the 2004 revisions led to the authorisation of an additional 25-30 innovative medicines in total across the 4-year window between 2006 and 2009.

Working with this estimate, we have assumed that those 25-30 new medicines will have been approved for sale in the EU and that each will have delivered 10 years of additional benefits to health services and patients. Our analysis of IQVIA sales data for the period 2009-2021 calculated an average annual sales income of €22.7m across all innovative medicines and all EU markets. Using this simple average figure for sales, we calculated the combined EU sales for these additional products falling in the range €570m-€680m. Based on the number of additional products and EU sales, we estimate the 2004 revisions were associated with an additional 170,000-210,000 QALYs across the period, based on a median ICER of €33k / QALY that was calculated using a basket of 11 medicines and the ICERs presented in the NICE HTA assessment reports.

Using the WHO guidelines on valuing a QALY (1-3 GDP/Capita),[30] as recommended in the Better Regulation toolbox (tool #31), and using an average GDP/capita for the EU of €27,810 (Eurostat Statistics Explained, 2021), we estimated the monetary value of the 2004 revisions would fall in the range €4.8bn-€17.2bn.

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[26] The Better Regulation Tool # 31 lists QALYs as one of the key non-monetary approaches for assessing health impacts. However, there are challenges when working across different patient populations and countries and across different interventions. For example, the same treatment can have markedly different costs across member states and can have markedly different benefits across patient groups (e.g. younger versus older citizens with less good underlying health). See Kocot, E., Kotarba, P. & Dubas-Jakóbczyk, K. The application of the QALY measure in the assessment of the effects of health interventions on an older population: a systematic scoping review. *Arch Public Health* **79,** 201 (2021).

[27] Data from Eurostat on Mortality and life expectancy statistics, as of 25 April 2022.

[28] According to the 2020 Annual Report on EudraVigilance for the European Parliament, the Council and the Commission, at the end of 2020, this database (the so-called "Article 57 database") contained information on more than 900,000 medicinal products (including different formulations and strengths as separate medicines).

[29] All holders of marketing authorisations for medicines in the EU and the EEA must submit information to the EMA on authorised medicines and keep this information up to date. This is a legally binding requirement from the EU pharmaceutical legislation. The Agency uses this information to support the analysis of data, regulatory activities, and communication.

[30] http://www.who.int/choice/cost-effectiveness/en/

Businesses

There are two types of cost impacts for businesses (EU-based pharma industry and wholesalers):

- One-off adjustment costs
- Recurrent adjustment costs

One-off adjustment costs are related to the changes that companies needed to make in order to be able to provide the information for the additional inspections introduced with the 2004 revisions. The interviews and surveys revealed that these costs were mainly related to the need to invest in upgraded IT systems. The survey delivered limited information on this. Based on the data received in the survey, we estimated the one-off costs at €250 million.[31]

Industry also incurred ongoing additional administrative costs associated with several of the new measures, including for example the expansion in the scope of the centralised procedure. Moreover, the revisions included changes to the submission documents (primarily the introduction of the environmental risk assessment [ERA], but also the introduction of the Summary Product Characteristics (SmPC) within the application and the need to improve the readability of the content of the package leaflet and label) and required much greater detail on manufacturing value chains and sites. The biggest additional costs however related to the post-market authorisation phase, with substantial additional reporting introduced to strengthen pharmacovigilance. Industry respondents were not able to provide specific estimates for these individual elements.

For originators, the additional costs amounted to ca. 5-10% increase in companies' regulatory costs. For the generics industry, the greater detail in the regulatory dossier increased the costs associated with notifications of revisions. The major drivers of the ongoing costs for the distribution industry are related to the need to control, record, and validate all the elements in their storage and distribution systems.

We have estimated these ongoing additional costs at €200m a year or €3bn over 15 years in current prices. Adjusting this for inflation would suggest a total cost of €2bn-€2.3bn.

We identified no significant, quantifiable indirect costs for industry. We had hypothesised that the revisions would have led to more general changes in company operations outside the regulatory department. We had for example anticipated the revisions causing developers to invest more heavily in later-stage clinical trials to secure the evidence necessary to meet the exacting standards of the EMA committees, but this was not confirmed in practice. Feedback from several generics companies does suggest that the Bolar exemption had a positive impact on their product development and earlier launch activities, however, this is a qualitative rather than quantitative observation, with no basis for estimating a quantitative impact.

On the benefits side, there were efficiency gains for companies in the guise of faster and more consistent assessment procedures (through the CP) and increased harmonisation of the decentralised procedures being run in different member states. For industry, however, the most significant efficiency gain relates to the withdrawal of the obligation to renew marketing authorisations every five years. We estimate these savings amount overall to around €300m-€375m over the past 15 years.

There are also small cost savings for businesses, due to faster (and thus less costly) approval procedures, through both the expansion of the central procedure and the introduction of the harmonised decentralised procedures (DCP), instead of the more variable national procedures that were in use prior to 2004. Based on the average number of new applications these savings are

[31] Five businesses estimated their one-off costs, which ranged from €25k to €15m, or 0.1-1% of annual sales. The median figure was around 0.5%. Applying this 0.5% to the EU pharma industry output in 2005 (c. €150bn according to EFPIA statistics), we arrive at an estimated gross cost of around €750m. There would have been a benefit to companies from implementing these new IT systems, and as such we have assigned a part and not all those costs to the 2004 revisions. We have no feedback as to the appropriate fraction, so we have assumed one third, or €250m, as a conservative estimate of the one-off costs for EU industry adjusting to the requirements of the legislation.

estimated at €40m per year across the period, with 90% of those savings being realised by the generics industry (c. €36m pa).

A second source of costs savings for business relate to the abolition of the 5-year renewal of marketing authorisations. The cost reduction of this is estimated at €23m per annum, covering both the MA holders authorised via the EMA and those authorised by member states. We estimate that this has resulted in a reduction of around 150 EMA renewals annually over the period, and 1,350 NCA renewals. Our stakeholder consultation confirmed that these changes had benefited the generics industry in particular, with its almost total reliance on national authorisation procedures and the abolition of all 5-yearly renewals for off-patent medicines containing well-known molecules. This has resulted in a saving of around €6.8m p.a. in fees and staff costs for the 150 EMA renewals, and around €16.2m for products authorised by member states, where the dossiers were less complex and renewal fees are lower. Taking these two cost items together, the net annual benefit for all companies would be on the order of magnitude of €23m a year.

Our consultations and desk research suggest the legislation has had no significant measurable impact on the EU pharmaceutical industry's overall performance, in terms of its economic output, medicines pipeline or global competitiveness. We had anticipated that several of the revisions might have encouraged and rewarded an increase in R&D, whether that was the extension of the period of regulatory data protection across all EU member states, the expansion in the provision of scientific advice to applicants, the provision of additional data protection for new indications or the introduction of new assessment procedures designed to cope with the evolution in medical science. Feedback from stakeholders suggest that these various positive changes would likely have been lost in a broader set of market pressures affecting the global research-intensive pharm industry. The statistics (e.g. BERD, medicines pipeline) for the EU broadly mirror the trends in the statistics for the US and other competitor regions, with no evident discontinuities in trends in the years following the implementation of the 2004 revisions. The one exception is biosimilars, where the EU regulatory system's early response has underpinned a comparative advantage. Data show that the EU accounted for around 70% of the world's biosimilar authorisations in the 5-year period 2006-2010. In 2016-2020, it still accounted for the largest share of authorisations (30%), albeit India and China have registered stronger growth and have bigger pipelines (Troein et al., 2021).

In summary, we estimate that the overall costs of the revisions to the EU pharmaceutical industry amounts to €1bn-€1.3bn. While this is a significant sum viewed in isolation, it amounts to around 0.5% of the EU industry's c. €200bn annual economic output and less than 0.05% of the total output over the 15-year period since 2004 (EFPIA & PWC, 2019).

Public authorities

The European Medicines Agency

The 2004 revisions led to a substantial increase in the work of the European Medicines Agency (EMA), related to the expansion in the scope of the central authorisation procedures and an intensification in respect to the provision of scientific advice and greater support for a wide range of coordination and development activities with respect to the regulatory network and international cooperation. The Agency's annual expenditure increased from €96m in 2004 to €266m in 2014, reflecting in part the further enlargement of the EU (10 countries joined on 1 May 2004) and the incorporation of these countries' national competent authorities within the EMA structures, and in part the intensification and transfer of authorisation activities from member states.

The EMA annual budget summaries are presented in the annexes to the Agency's annual reports (European Medicines Agency, n.d.-b) and show steady year-on-year growth across the 10 years to 2014 and beyond. The distribution of activities has remained broadly stable over time, split 35% on staff costs (Title 1), 25% on buildings (Title 2) and 40% on operations (Title 3). Operational expenditure (Title 3; mainly consisting of expenditure for meetings [c. 4% of all Title 3 costs] and evaluations [c. 35% of all Title 3 costs]) for EMA increased from €39m in 2004 (European Medicines Agency, 2005) to €168m in 2020 (Samassa, 2021), while staff expenditure (Title 1) increased from €32m to €115m in the same period. Both types of expenditure rose much faster than inflation in these years (while prices in the Eurozone have risen by 29% across the whole of this 15-year period).

The increase in real terms was thus around €190m in the period 2004-2020, for Title 1 and Title 3 combined.

This increase may be partly, though not wholly, attributed to the 2004 revisions. In the absence of these additional EMA-led procedures, businesses would have continued to make use of national procedures. This means that NCA-led authorisations are lower due to expansion of the centralised procedure. We assume these national savings largely mirror the extra costs for EMA. There may be economies of scale, however, the amount to which these MS savings and EU costs differ proved difficult to assess, as our data collection has not resulted in clear indications from stakeholders about either the savings or the costs. Given the intensification of support and coordination that accompanied the transfer of activities from the national regulators to the EMA, we estimate that around 20-25%, or €40m-€50m, of the real-terms increase in EMA expenditure (Title 1, Title 3) is related to the 2004 revisions. We base this estimate on the fact that about 20-25% of all EPAR/opinion entries on the EMA website are non-paediatric and non-orphan related. Given the substantial increase in EMA costs over time, and the need to make assumptions about attributable impacts, we have worked with an average annual additional cost in the range: €2.5m-€3.1m.

National authorities

Most NCAs provide assistance to the EMA through the release of staff to work within its main committees and working parties, supporting both the assessment of applications and post-authorisation activities (e.g. variations, renewals, translations, etc.), whereby the expansion in the scope of the work of the EMA had resulted in a reduction in activities relating to national authorisations and a switch to work in support of the EMA.

Only two NCAs attempted to quantify the changes to their costs due to the 2004 revisions. Several other NCAs reported increases in national costs relating to the expansion of EMA activities in general (the expanded scope of the CP) and in particular the additional enforcement obligations due to the strengthened pharmacovigilance system, however, these stakeholders were not able to quantify those additional costs.

The two estimates provided by the NCAs, for their annual additional costs, fell in the range of €165k-€500k. To estimate the likely total cost for the EU overall, these two smaller EU member states account for around 1.3% of the EU population, and assuming these additional costs are typical, would mean that the additional annual costs for national regulators across the EU would have fallen in the range €12.7m-€38.5m per annum. The EMA reimburses the NCAs for certain activities, whereby the costs associated with these additional national activities are covered in part by the EMA financing. To avoid double counting, we have discounted these estimates by 35%. One of the two NCAs estimated that the EMA reimbursement covered 25-35% of its costs in the period, resulting in an indirect subsidy from national regulators. Applying this discount of 35%, would mean that the additional annual costs for national regulators across the EU fall in the range €8.2m-€25m per annum. Neither of the NCAs that provided an estimate of the additional costs incurred provided a breakdown of costs split between their support for assessments and post-marketing authorisation activities. One of the two did indicate that post-marketing authorisation aspects comprise around 80% of their total EMA-related activities, and if we assume the additional costs are equally distributed, that implies additional annual costs of €1.65m-€5m for NCA support for EMA-related assessment activities and €6.6m-€20m for post-authorisation activities.

Several national regulators commented on the benefits of the switch to the DCP and the use of a more streamlined and harmonised set of authorisation procedures, however, no estimates were offered as to the scale of any cost savings. We reviewed the annual financial accounts of several national competent authorities, which revealed increases in both fee income and staff / operating expenditure in the period 2005-2010, however, those financial accounts offered no view on any efficiency gains relating to changes in authorisation procedures. We have therefore made a conservative estimate of a 1-2% improvement in efficiency for all NCAs resulting from the streamlining measures, which we estimate as resulting in €20m-€40m savings annually.

4.1.2.3 Societal impacts

The 2004 revisions did introduce the environmental risk assessment (ERA) within the application documents, albeit it did not have a bearing on the authorisation opinion. Industry respondents

suggested that this had improved transparency (around the specific risks associated with the molecules / APIs of new medicines) and increased awareness of those environmental risks amongst manufacturers and their supply chains. However, these are small, incremental improvements, and the EU pharmaceutical industry's carbon footprint has not been affected directly, positively, or negatively, albeit indirectly, the high-quality regulatory environment has supported the expansion of the industry and an increase in greenhouse gas emissions. Expansion has also been driven by global consumption of medicines, and the industry has a particularly high carbon footprint that is a growing focus for improvement measures (Ray et al., 2021).

4.1.2.4 Simplification and burden reduction

The preceding paragraphs have detailed three areas of simplification and burden reduction that have been realised following the implementation of the 2004 revisions, which we have captured in the table below, in line with the table presented in the Better Regulation toolbox (Annex III Table 2):

- Cost savings for industry, and especially the generics industry, due to the harmonisation and streamlining of procedures associated with the introduction of the DCP and the substantial reduction in the use of the MRP
- Cost savings for industry, and especially the generics industry, due to the switch to a single renewal of a MA 5 years after the original notice of authorisation, eliminating the need for further renewals at 5-yearly cycles, and removing the need for renewals by generics companies
- Cost savings for NCAs due to streamlining / harmonisation of national authorisation procedures (switch to DCP away from MRP)

In addition to the reduction of burden achieved, there are also evident opportunities for further reductions of administrative burden going forwards.

Our stakeholder consultations revealed widespread concerns across industry and regulators about the under-exploitation of digitalisation within the EU pharma regulatory system and the related problem of duplicative activity. As such, there may be areas where further harmonisation and digitalisation of regulatory processes could deliver savings, however, these are contingent on future revisions and operational enhancements being implemented. As an aside, we note that the EMA strategy indicates there are >80 people working on digital transformation and its annual financial accounts show it is investing €5m-€15m a year in new ICT systems. The wider literature on ICT productivity suggests that a 10% increase in ICT investment should produce a productivity gain of around 0.6% (Cardona et al., 2013). We have used this general factor applied to the main regulatory cost components borne by industry and the EU and national administrators to estimate the potential annual savings:

- Industry: we estimate potential annual savings of €9.6m, assuming an EU-wide regulatory budget of around €1.6bn, we estimate the wide-ranging implementation of enhanced ICT solutions, open data and worksharing
- EMA: we estimate potential annual savings of €2.1m, assuming an annual EMA budget of around €350m, we estimate the wide-ranging implementation of enhanced ICT solutions, open data and worksharing
- NCAs: we estimate potential annual savings of €12m, assuming an EU-wide budget for NCAs of around €2bn, we estimate the wide-ranging implementation of enhanced ICT solutions, open data and worksharing

4.1.2.5 A harmonised system of regulatory data protection

The 2004 revisions introduced a harmonised system of regulatory data protection for innovative medicines (8+2+1) that stakeholders viewed positively, with the new arrangements bringing greater clarity, harmonisation and predictability as compared with the previous situation, where there were a variety of different national policies in place.

The baseline situation was defined by Directive 87/21/EEC, which required EU member states to provide a period of six years of data exclusivity for most pharmaceuticals starting at the date of the first market authorisation, and 10 years for biotech and other high-tech medicinal products (Adamini et al., 2009). The Directive allowed member states to define a period of ten years for all pharmaceuticals if they considered this "in the interest of public health." Belgium, France, Germany,

Italy, the Netherlands, Sweden, and the United Kingdom did so, the other eight member states implemented the 6-year period as their default term, using the 10-year period selectively. The 2004 revisions turned the 6-year and or 10-year period into the 8+2 arrangements and made it applicable across all 15 MS and the 13 central and eastern European countries that joined the union in May 2004. The latter typically had no specified period of data exclusivity, prior to this. While more than half the EU would have seen an enhancement in the standard period of regulatory protection, most innovative medicines – even nationally authorised – would have been granted 10 years protection rather than six.

We tried to explore the extent to which this harmonisation of regulatory data protection had produced additional costs or benefits, using the IQVIA sales data, however, we found that the effects of the 2004 revisions did not materialise until much later and with EU expansion, the new countries added individual rules to the system, so it proved impossible to make a quantitative comparison with the 1987 baseline. In practice, we have had to use a difference baseline, comparing trend data on EMA authorisations across the 2000s, with equivalent trend data for the FDA. This does reveal a measurable and positive effect on the EU's relative output of innovative new medicines in the years following the implementation of the revisions.

Industry stakeholders noted that this aspect of the 2004 revisions had contributed to the attractiveness of the EU's regulatory system globally. Our international comparative legal analysis confirmed the continuing relative advantage of the innovation incentives within the EU system as compared with those in operation in selected other regions, as did the international review reported by Copenhagen Economics (2018).[32] Several stakeholders from patients' groups and academia remarked on what they considered to be the overly generous provisions available within the EU, which they argued have favoured innovation over access. These same groups recommended the EC review the balance between innovation and access in the related Impact Assessment, suggesting there is scope to reduce innovation incentives without damaging Europe's attractiveness globally while also strengthening the rewards / obligations around access and affordability.

4.1.2.6 Proportionality of costs and benefits

The table of costs and benefits shows that the 2004 revision is likely to have resulted in a net increase in regulatory costs to society on the order of €1.1bn-€1.8bn (over 15 years). The higher costs are the result of the higher standards set and the associated additional compliance and regulatory costs.

There have also been benefit gains in terms of reduced costs for MAHs, the EMA and NCAs, which sum to €1.2bn-€1.5bn, largely offsetting the additional costs of increased information requirements and pharmacovigilance activities.

The 2004 revision is also widely believed to have resulted in more innovative medicinal products and a higher quality regulatory system, which is likely to have resulted in a positive health impact for patients treated with such products, which would otherwise not have been available, or would have been available later in time. We have estimated this additional health impact at 25-30 new innovative medicines, in total; producing 170,000-210,000 QALYs in total; which amounts to €4.8bn-€17.2bn in monetised benefits, using WHO guidelines on valuing QALYs.

The valuation of health impacts is widely accepted to be deeply challenging and was carried out at an aggregate level, however, even working with the lower bound estimate of health impacts and cost savings (€6bn) and the upper bound of the estimated additional costs (€1.8bn), the 2004 revisions have delivered a positive overall social return.

This economic analysis resonates with feedback from stakeholders overall, where the overall balance of opinion is positive: the costs of the revisions are judged to have been proportionate to the benefits. The overall positive opinion as to the cost-effectiveness of the legislative changes, looks different across stakeholders. Industry and public authorities are strongly positive on the overall balance of costs and benefits, whereas health systems and – in particular – patient groups are slightly negative overall. The latter consider the legislation has been strongly beneficial to industry, with the revisions

[32] See pages 53 and 54 of the study.

offering valuable incentives that have supported investment in innovative medicines but have increased prices for those products. They are very much less positive about the balance of costs and benefits from the patient's perspective, expressing concerns about affordability, uneven access, unmet medical needs, and medicines shortages. For this group, the perceived health impact is relatively small as compared with the (indirect) costs of the 2004 revisions and the substantial number of remaining challenges.

4.1.2.7 The costs of partially meeting or not meeting some of the objectives

The 2004 revisions have achieved their objectives in large part, and as such there have been no substantial costs incurred by any stakeholder groups associated with a failed or partially achieved objective. There is arguably an issue around access and affordability in the broadest sense, where the 2004 revisions did little to improve the effectiveness of the general pharmaceutical legislation in ensuring access to medicines for all; and while it was not a specific objective there are widespread concerns that medicines shortages have become a bigger problem over time. Shortages were seen as a large cost to public health and for day-to-day operations. Pharmacists in particular argued that the legislation lacks flexibility to allow them to handle shortages, which creates inefficiencies. It was estimated by some interviewees that pharmacists spent 6 hours every week to deal with medicine shortages, though the average in Portugal can be as high as one day per week spent on this task. For Public authorities and Civil society organisations, the high price of medicines arising from what they judge to be the misuse/abuse of incentives was cited as a cost to healthcare systems, in particular for small countries.

4.1.2.8 The main costs and drivers of the legislation

The 2004 revisions implemented a series of measures that have contributed to improvements in the effectiveness of the regulatory system, while also having been successful in delivering important efficiency gains for the EU's general regulation of pharmaceuticals.

Several measures stand out as having contributed efficiency gains, including:

The definition of medicinal products, which was adapted to take account of new therapies and their method of administration and provide a new pathway for biosimilar medicines
The expansion in the scope of the centralised authorisation procedure
Introduction of the decentralised authorisation procedure and optimisation of mutual recognition procedure for nationally authorised products together with optimised referral procedures
Reduced administrative burden by withdrawal of obligation to renew marketing authorisation every five years and introduction of sunset clause on validity of marketing authorisation

The 2004 revisions also introduced various new measures, designed to improve the effectiveness of the regulatory system overall, that brought additional costs for some stakeholder groups.

- Changes to documentation requirements, including environmental risk assessment (ERA)
- Increased transparency and harmonisation of key documents, i.e. the EMA began to publish European Public Assessment Reports (EPARs), which are publicly accessible information resource comprising a summary suitable for lay audiences alongside a series of regulatory documents regarding the MA holder, the product (e.g. summary of product information (SmPCs) and package leaflet) and assessment history[33]
- Harmonised application of good manufacturing practice (GMP) for active substances
- Improved pharmacovigilance by more frequent submission of periodic safety update reports (PSURs), which resulted in additional costs for MA holders and regulators
- Reinforcement of inspections with improved coordination by introducing new tools (EudraGMDP database), which brought efficiency gains through improved information exchange among regulators but has created some additional burden for MA holders that must maintain the currency of large numbers of records with frequent changes required with respect to what are inevitably dynamic global supply chains and distribution networks.

[33] Setting up and maintaining the document archive, drafting overviews and upgrading the existing individual components into a publishable suite of consistent and commercially non-disclosive documents involved the EMA in some limited additional costs.

Table 4 Summary of estimated costs savings and potential future savings

PART I **Simplification and burden reduction (savings already achieved)**

Cost savings		**Citizens / Consumers**	**Citizens / Consumers**	**Businesses**	**Businesses**	**Administrations**	**Administrations**
		Quantitative	**Comment**	**Quantitative**	**Comment**	**Quantitative**	**Comment**
Compliance costs: MAH savings	**recurrent**	-	-	CP: €4.8m p.a., DCP: €36m p.a.	Cost savings due to the harmonisation and streamlining of procedures associated with the introduction of the DCP and the substantial reduction in the use of the mutual recognition procedure	-	-
Compliance costs: MAH savings	**recurrent**	-	-	€23m p.a.	MA holders benefited from the switch to a single renewal of a MA 5 years after the original notice of authorisation, eliminating the need for further renewals at 5-yearly cycles, and removing the need for renewals by generics companies	-	-
Enforcement savings (NCAs)	**recurrent**	-	-	-	-	€20m-€40m pa	Cost savings for national competent authorities due to streamlining / harmonisation of national authorisation procedures (switch to DCP away from MRP)

PART II **Identify further potential simplification and savings that could be achieved with a view to make the initiative more effective and efficient without prejudice to its policy objectives.**

Direct benefits		**Citizens / Consumers**	**Citizens / Consumers**	**Businesses**	**Businesses**	**Administrations**	**Administrations**
		Quantitative	**Comment**	**Quantitative**	**Comment**	**Quantitative**	**Comment**
Compliance costs: MAH savings	**recurrent**	-	-	9.6	There are opportunities for substantial further digitalisation across the EU pharma regulatory system to increase efficiency and duplicative activity	-	-

Enforcement savings (EMA)	**recurrent**	-	-	-	-	2.1	There are opportunities for substantial further digitalisation across the EU pharma regulatory system to increase efficiency and duplicative activity
Enforcement savings (NCAs)	**recurrent**	-	-	-	-	12	There are opportunities for substantial further digitalisation across the EU pharma regulatory system to increase efficiency and duplicative activity

Administrative complexity and costs

In carrying out the evaluation, and the analysis of costs and benefits, we have sought to identify the elements of the general pharmaceutical legislation that pose an administrative burden or were overly complex.

For industry, the major administrative burden relates to the additional post-market authorisation procedures that have to be followed in order to support a more robust pharmacovigilance system (partially out of scope of the current evaluation).

For public authorities, the major additional costs were associated with the expansion in the scope of the centralised procedure and the general intensification of the work of the EMA committees. This however is largely driven by increasing applications. There have also been challenges with the growing numbers of advanced therapies and more complex products that require relatively greater scientific effort to review and often entail assessments and advice from multiple committees.

For national health technology assessment agencies and health payers, the introduction of the CMA had proved problematic, with substantial additional costs associated with the subsequent assessment of the relative cost-effectiveness of newly authorised medicines. The uncertainty associated with fewer data has led to later challenges on cost-effectiveness and is causing some HTAs to not approve medicines for reimbursement where the evidence is particularly difficult.

4.1.3 Coherence

The criterion of coherence of the legislation refers to both how the various elements of the legislations work internally and how these are complementary (or duplicative) with other EU policies to achieve the legislation's intended objectives.

Coherence has thus been approached and considered in three elements, 1) internal coherence 2) coherence with specialised pharmaceutical legislation 3) coherence with other EU legislations. In the following we respond to the evaluation questions posed in the terms of reference of the study. For a full analysis, see Annex IV.

4.1.3.1 Internal coherence

The legal analysis and literature review on the EU general pharmaceutical legislation has not led to the identification of overlaps, contradictions, or other inconsistencies between the Directive and the Regulation despite the fact that they cover different authorisation procedures as illustrated in the table below. The Directive and Regulation contain multiple cross-references and common requirements (e.g. same definitions, some prohibitions for non-authorised medicinal products).

Table 5 Mapping of cross-references between Directive 2001/83/EC and Regulation (EC) No 726/2004

Directive 2001/83/EC	Cross-reference to Regulation (EC) No 726/2004
Article 6	The prohibition to put in place a medicinal product without a marketing authorisation including the one granted in accordance with Regulation (EC) No 726/2004
Article 11	Medicinal products granted under Regulation (EC) No 726/2004 in accordance to its Article 23 must contain a summary of product requiring a specific statement and symbol
Article 23	The marketing authorisation holder must ensure that the product information is kept up to date with the current scientific knowledge including with information diffused on the EMA web-portal on medicinal products authorised in the Union as set under Article 26 of Regulation (EC) No 726/2004
Article 27	The coordination group must rely on the scientific assessment and the recommendations of the Pharmacovigilance Risk Assessment Committee provided for in Article 56(1) (aa) of Regulation (EC) No 726/2004 as part of EMA and that this coordination group must apply the rules under Article 63 of this Regulation on conflict of interest and transparency
Article 57	Member States when setting labelling requirements on price, reimbursement, legal status for supply to the patient concerning medicinal products authorised under

	Regulation (EC) No 726/2004 must observe the detailed guidance referred to in Article 65 of this Directive
Article 59	Additional statements required for medicinal products included in the list referred to in Article 23 of Regulation (EC) No 726/2004 which are subject to additional monitoring.
Article 76(2)	Medicinal products subject to wholesale distribution and storage must be covered by a marketing authorisation granted pursuant to Regulation (EC) No 726/2004 or by the competent authorities of a Member State in accordance with this Directive.
Article 85(B)	Persons brokering medicinal products shall ensure that the brokered medicinal products are covered by a marketing authorisation granted pursuant to Regulation (EC) No 726/2004 or by the competent authorities of a Member State in accordance with this Directive.
Regulation (EC) No 724/2004	**Cross-reference to Directive 2001/83/EC**
Article 2	The definitions laid down in Article 1 of Directive 2001/83/EC and those laid down in Article 1 of Directive 2001/82/EC shall apply for the purposes of this Regulation.
Article 3(3)	A generic medicinal product of a reference medicinal product authorised by the Community may be authorised by the competent authorities of the Member States in accordance with Directive 2001/83/EC and Directive 2001/82/EC under certain conditions
Article 6	Each application for the authorisation of a medicinal product for human use shall specifically and completely include the particulars and documents as referred to in Articles 8(3), 10, 10a, 10b or 11 of, and Annex I to, Directive 2001/83/EC. […]
Article 12	Authorisation shall likewise be refused if particulars or documents provided by the applicant in accordance with Article 6 are incorrect or if the labelling and package leaflet proposed by the applicant are not in accordance with Title V of Directive 2001/83/EC.
Article 13	Without prejudice to Article 4(4) of Directive 2001/83/EC, a marketing authorisation which has been granted in accordance with this Regulation must be valid throughout the Community. It shall confer the same rights and obligations in each of the Member States as a marketing authorisation granted by that Member State in accordance with Article 6 of Directive 2001/83/EC. [...]
Article 19	The supervisory authorities shall be responsible for verifying on behalf of the Community that the holder of the marketing authorisation for the medicinal product for human use or the manufacturer or importer established within the Community satisfies the requirements laid down in Titles IV, IX and XI of Directive 2001/83/EC.

The findings from legal analysis and literature review are supported by the feedback received from the different stakeholder consultations. None of them, including public authorities who are in charge of implementing it and therefore major actors concerned, mentioned coherence issues. On the contrary, several stakeholders consulted explicitly mentioned the good internal coherence of the EU general pharmaceutical legislation (public authorities, industry, healthcare professionals).

More specifically, the targeted surveys indicated that respondents found the legislation moderately coherent internally. Industry rated the internal coherence the highest out of the stakeholder groups while academics the lowest with a lack of consensus within that stakeholder group. When asked about the most and least coherent aspects of the legislation in the targeted surveys or for additional comments in the public consultation, responses focussed on coherence of the legislation with specialised and complementary legislations rather than the internal coherence of the legislation itself. Within the interviews, respondents across all the stakeholder groups were generally positive about the internal coherence of the legislation remarking that there were no major problems and that the components of the legislation were synergistic.

4.1.3.2 Coherence with specialised pharmaceutical frameworks

There are several in-built mechanisms to ensure an adequate articulation between the general pharmaceutical legislation and the specialised pharmaceutical frameworks[34].

Nevertheless, some potential issues of coherence with the specialised pharmaceutical frameworks were identified. For instance, under the **Paediatric Regulation**, the differing national rules on the conduct of trials with children may still delay the completion of a paediatric investigation plan (PIP)[35], hampering the achievement of better compliance checks for PIPs. This may undermine the complementarity of this legislation with the general pharmaceutical legislation. The **Orphan Regulation** does not interact in a coherent fashion with Directive 2001/83/EC as regards generics entry. For orphan medicinal products, generic competitors can only submit an application for marketing authorisation at the end of the 10-year protection period while in general, for all human medicines, at the end of that period generic competitors can directly place generics on the market. Finally, a lack of coordination between the Committee for Medicinal Products for Human Use, on the one hand, and the Paediatric Committee, the Committee for Orphan Medicinal Products and the Committee for Advanced Therapies, on the other hand was identified[36] .

4.1.3.3 Coherence with linked legislation

There are several pieces of legislation not included in the specialised pharmaceutical legislation whose implementation can impact on several objectives of the general pharmaceutical legislation.

Linked legislation on health matters

The **EMA fees Regulation** provides the fees for the various procedures of authorisation and acts in parallel with the general pharmaceutical legislation, i.e. rules underlying the fee system are set by the general pharmaceutical legislation. An efficient fee system helps to ensure quality, safety and efficacy of medical products by creating a robust authorisation system. Nevertheless, according to public authorities and industry respondents, this objective could be hampered by the fact that NCAs are no longer adequately compensated, and this would lead to an authorisation system that is not cost-effective.

The **BTC legislation** raises other concerns. Here the main issue lies in classification, given the difficulties to define a substance/product as a BTC or as a medicinal product. Revision of the BTC legislation foreseen for 2022 aims to address this issue by improving clarity and aligning safety, quality, and efficacy standards to those in the pharmaceutical and medical devices regulation. Similarly, under the **Medical Devices Regulation** difficulties arise when a medical device incorporates substances which if used separately can be considered medicinal products, thus creating a classification issue. The incoherence, raised also unanimously by stakeholders which call for a harmonisation of definitions and processes, is centred around unclear definitions, differing interpretations and regulations between MSs. A reduction of disparities is therefore needed, to create a level playing field between MSs and facilitate free movement of medicinal products through more harmonised processes. The Medical Devices Regulation also raises another concern. EMA remains the only major pharmaceutical regulatory body that is not in charge of medical devices. Thus, a point of contention is whether the pharmaceutical legislation is coherent with the Medical Devices Regulation when the latter has apparently less demanding regulatory standards, affecting the relative safety profiles of drugs and devices (Pane et al., 2017). The tensions are particularly strong for drug-device combination products, and clinical pathways where a device or drug could be recommended. The disparity in regulation could distort medical markets, put pressure on patient safety and access, and generate other inefficiencies from lack of integration.

[34] (e.g., Article 2, 7, 27, 47 of Regulation (EC) 1901/2006; Article 10a (1) of Regulation (EC) 141/2000; Article 8(3) and 3(7) of Directive 2001/83/EC); without prejudice clauses (e.g. Article 2 or Regulation (EC) 1394/2007) and derogations (e.g. Article 9 of Regulation (EC) 1901/2006; Article 10 to 13 of Regulation 1394/2007).

[35] COMMISSION STAFF WORKING DOCUMENT EVALUATION Joint evaluation of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products. SWD/2020/0163 final

[36] COMMISSION STAFF WORKING DOCUMENT EVALUATION Joint evaluation of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products

The **Health Technology Assessment Regulation** contains proper legal coordination mechanisms with the general pharmaceutical legislation. It therefore appears unlikely that the Regulation will limit the realisation of the general pharmaceutical legislation. It may even contribute to ensure the quality, safety and efficacy of medicinal products and reduce duplication of efforts for manufacturers. However, implementation aspects could reveal areas of tension.

The **Cross-border healthcare Directive** has several legal interlinkages with the general pharmaceutical legislation. This Directive is essential to achieve the objective of ensuring an equitable access to medicines. Therefore, two aspects should be clarified: whether the 'restricted' medical prescription foreseen in the Directive 2001/83/EC should be recognised under the Cross-border healthcare Directive and what kind of classification for the dispensing of homeopathic medicinal products is meant in Article 14(1) of Directive 2001/83/EC, to understand how it could affect the recognition of prescriptions under the Cross-border Healthcare Directive.

Significant issues of coherence with the **GMO (Genetically Modified Organisms) legislation** have been identified. These issues may limit the realisation of several objectives of the general pharmaceutical legislation. Medicinal products containing GMOs do not fall under the scope of application of the GMO legislation, but the EMA or national authorities conduct the assessment in accordance with the GMO legislation, which supports the idea of a reduced administrative burden for applicants. Furthermore, the GMO legislation, through its own objectives, supports the general pharmaceutical legislation's objective of ensuring the safety of medicinal products. However, the pursuit of this safety objective is limited by the different national approaches to GMO legislation in medicinal products, in particular regarding the possibility offered in the general pharmaceutical legislation for MSs to authorise the supply of a medicinal product in cases of compassionate use, including medicinal products containing GMOs.

Both the **BSSD (Euratom Basic Safety and Standards Directive)** and the general pharmaceutical legislation apply to radiopharmaceuticals leading to potential issues of coherence (e.g., lack of specialised definitions for radiopharmaceuticals and their associated technologies, inconsistencies with dosage requirements, difficulties linked to the authorisation procedure). This creates a challenging environment for the development and roll-out of radiopharmaceuticals in the EU and thus impacting several objectives of the general pharmaceutical legislation and in particular access to medicines, global attractiveness and innovation.

The **Regulation on food additives** applies to medicinal products and directly impacts the possibility of manufacturers of medicinal products to use certain substances as food additives in medicinal products. Thus, the linkage of food legislation supports the realisation of the pharmaceutical legislation's objectives of ensuring the safety of medicinal products, although it could in theory limit competitiveness and/or innovation.

The **Transparency Directive** is legally coherent with the general pharmaceutical legislation. However, a weak enforcement of the rules of the Directive, as well as the lack of detailed specific requirements on the information to be provided by MAHs in pricing and reimbursement applications can limit the transparency of the process, and ultimately impact the policy objective of access to medicines.

Linked legislation not directly linked to the health sector

The interplay between the IP rights of the **SPC legislation** and the regulatory exclusivity rights of the general pharmaceutical legislation has been described by stakeholders consulted as complex and suboptimal, and fragmented across MSs. This may impede the general pharmaceutical legislation's objectives of achieving attractiveness of the European market in the global context as well as of reducing administrative burden and duplication of efforts. Furthermore, the possibility of evergreening/overcompensation practices may lead to reduced access to medicines, in view of the delayed entry of biosimilars and generics. In general, IP/data protection rules have the potential to limit the possibility of compulsory licensing, thus limiting action in favour of access to medicines. Regulation (EU) 1257/2012 on a **Unitary Patent protection** will create synergies between patent protection and centralised authorisation of medicinal products, thus increasing attractiveness of the European market, reducing administrative burden, disparities and duplication of efforts, while facilitating the free movement of medicinal products.

Data protection laws are coherent with the general pharmaceutical legislation in terms of scope, considering the horizontal aspect of the GDPR/EUDPR covering all activities linked to research on and manufacture of pharmaceuticals. However, the data protection legal framework can create specific limitations to the general pharmaceutical legislation's objectives of accommodating innovation, i.e., for research, due to possible conflicts between their respective objectives (innovation and personal data protection). More specifically, there appears to be a lack of clear and uniform data protection framework and approaches for research, on several matters, hampering the conduct of clinical trials and reuse of data for future research.

The **drug precursor legislation** does not hamper the objectives of the general pharmaceutical legislation, in particular in light of the objective of access to medicines. However, the general pharmaceutical legislation may need to better control medicinal products containing (pseudo)ephedrine, which can be used to produce (meth)amphetamines and can be easily purchased without falling under the control mechanisms applicable to drug precursors.

Substances used in the manufacture of medicinal products are exempted from most part of **REACH Regulation**. This specific exemption regime ensures, inter alia, that REACH does not overlap with the general pharmaceutical legislation. Such exemption regime however raised some concern on the need to align the environmental risk assessment requirements under the general pharmaceutical legislation with the one under REACH. Stakeholders also pointed out limitations brought about by REACH to the production of APIs, potentially impacting the pharmaceutical legislation's objective of wide access to medicines in Europe.

Policy actions to mitigate the impact of medicinal products in water will be in place with the revision of the **Environmental Quality Standard Directive** (2008/108/EC as amended by 2013/39/EU), revision of the **Groundwater Directive** (2006/118/EC) and the revision of **Waste Water Treatment Directive** (91/271/EEC). However, this will imply additional compliance costs for MSs. Only a limited set of pharmaceuticals can be targeted effectively with this legislation (i.e. those monitored in most parts of the EU and posing the biggest risk to nature / human health), leaving the majority of pharmaceuticals unaddressed. As such, updates to guidance are necessary for effective monitoring of pharmaceuticals in water and information/coordination between authorities appears insufficient.

EU Competition law supports the realisation of two of the general pharmaceutical legislation's objectives since it aims at ensuring a competitive functioning of the EU internal market for medicinal products, by limiting the existence of dominant positions of e.g., originators, ensuring a dynamic competitive environment via the control of mergers, while improving access (and affordability) for patients. In fact, the Commission, in the Pharmaceutical Strategy, relies on competition enforcement as one of the instruments to achieve access to affordable and innovative medicines to European patients. The sanction of anticompetitive practices, e.g., abusive patent management, supports the general pharmaceutical legislation's objectives of ensuring a competitive functioning of the internal market, attractiveness in the global context, and accommodate innovation.

4.2 How did the EU intervention make a difference?

The EU added value resulting from the EU legislation is defined as the additional value of EU action compared to what could be achieved at national or regional levels alone. Overall, there was strong consensus among the different stakeholder groups that the general pharmaceutical legislation has large EU added value. Stakeholder consultations pointed to the **legislation providing a robust framework enabling harmonisation of regulations, incentives, standards, administrative requirements, and procedures for pharmaceuticals across the EU.** These centralised and coordinated harmonisation measures across the medicine lifecycle simplified the regulatory system for medicine developers and reduced duplication of efforts across MSs. Moreover, from the perspective of stakeholders, the centralised medicine authorisation procedure and post-authorisation surveillance has improved the availability of high-quality, safe, and effective medicines across MSs.

There was consensus that the legislation has struck the right balance between action at EU level and national action. In the targeted survey, stakeholders indicated this to be the case to a moderate to large extent (Table 6). In accordance with the EU added value of the legislation, respondents considered that in the absence of EU level action, member states would have been able to put in place appropriate measures only to a small or moderate extent.

Table 6. Overview for the evaluation criterion 'EU added value' summarising the overall average view for all stakeholders, per stakeholder group, and the level of agreement across the stakeholder groups.

Please provide your view on the balance of EU level actions and national actions arising from the legislation.	All stakeholders average score	Individual stakeholders average score					Agreement between stakeholders
		Industry	Civil Society	Public Authorities	Academic	Health Services	
To what extent has the legislation struck the right balance between action at EU level and national level?	3.3	3.2	2.8	3.37	3.7	3.3	High
To what extent has the EU intervention in the context of the COVID crisis struck the right balance between action related to the legislation at EU level and national level?	3.8	4.22	3.7	3.6	3.9	3.6	High
In the absence of EU level action, to what extent would member states have had the ability to put in place appropriate measures?	2.4	2.3	1.75	2.7	3.0	2.5	High

Source: Targeted survey data

Interviews with stakeholders and open survey responses highlighted that the **centralised procedure (CP) for authorisation of medicines has been a valuable mechanism to improve the availability of medicines across the EU**. The CP has been particularly valuable for smaller MSs without the necessary resources and expertise to establish their own systems – a view that was shared by public authorities in smaller MSs. Overall, stakeholders wanted greater use of CP across EU. However, some industry stakeholders highlighted the added value of having the decentralised procedure and mutual recognition procedure in addition to the CP, in order to allow flexibility to get approval of medicines at the MS level, in particular for SMEs and generic manufacturers.

Stakeholder groups, including industry and public authorities, highlighted the added value of **EU-level coordination and cooperation to develop best practices**. For example, industry stakeholders highlighted the EU as a global leader in establishing the first science-based regulatory framework for authorisation of high-quality, safe and effective biosimilar medicines. Another recognition of EU as a leader in regulatory practices was indicated by an academic stakeholder who pointed out that low- and middle-income countries have benefited from collaboration with EMA to strengthen their regulatory capabilities. For example, EMA has contributed mentorship in the ZaZiBoNa initiative, a collaboration between national medicines regulatory authorities in Africa (Sithole et al., 2020). While it is an unintended impact of the EMA's increasingly recognised international leadership role, it relies on pooling of scientific capabilities across Europe, partly attributable to the 2004 revision of the legislation.

Within interviews, stakeholders commonly cited the creation of the European Medicines Agency (EMA) as one of the biggest achievements of the legislation. Stakeholders regarded **EMA as a key actor in the unification and coordination of the regulatory system across the EU**. Furthermore, several stakeholders confirmed EU regulatory networks coordinated by EMA provide a valuable exchange of experience and access to a wide range of scientific and technical expertise, which would not be available in one country or region alone. Thus, **the pooling and coordination of scientific resources under a common set of rules and practices** has helped foster a common understanding across MSs on how medicinal products are evaluated and approved to a high standard and dealing with safety concerns in a consistent way. Industry stakeholders pointed to increased cooperation between MSs and public authorities and highlighted successful collaboration of EMA with NCAs that has led to the optimisation of their resource use. The pan-EU SPOR (Substance, Product, Organisation and Referential) data management services was cited as an example of a valuable resource for promoting exchange of medicinal product information across MSs.

Furthermore, interviewed stakeholders frequently pointed out that since the establishment of EMA, **transparency on how the regulatory system works and decisions are made has greatly improved** – thus building trust and consistency across the EU regulatory system. EMA publications of European public assessment reports (EPARs) and guidance documents were cited as a reason for the increased flow of transparent information. Industry stakeholders highlighted EMA's clear guidance on pre-authorisation and post-authorisation procedures for medicines were particularly valuable for facilitating regulatory processes. Moreover, EPARs have had wider impact in facilitating approval of medicines outside the EU (e.g. Africa, Asia, South America). An academic stakeholder highlighted

clinicians have also benefited from access to EPARs when making assessments on whether to prescribe medicines to patients.

4.2.1 Added value of the EU intervention in the context of the COVID crisis

EU action during COVID-19 crisis was a particularly value added intervention. In the survey, all stakeholders scored the extent of striking the right balance as large to very large (Table 6). In interviews, there was a common theme across stakeholders that EU level action **enabled quicker and concerted action** compared to what MSs would have been able to achieve independently. Stakeholders commonly cited this was made possible because of **regulatory flexibilities and optimisations** enabling resources, capacities, expertise, and IT capabilities to be rapidly mobilised across EU. For example, the Commission granted a temporary derogation from certain rules for clinical trials of medicines involving GMOs, in particular environmental risk assessment (Regulation (EU) 2020/1043 of the European Parliament and of the Council, 2020) and allowed remote processes for source data verification, audits and monitoring (European Medicines Agency, 2022b). Thus, accelerating the development and approval of vaccines and coordinating equitable access to vaccines in all MSs.

The pandemic provided an opportunity to display how the legislation enabled MSs to **work together, learn from each other and coordinate efforts**. For example, public authorities cited multinational work sharing activities such as assessments of COVID-19 vaccines as an EU added value – especially for less experienced MSs.

The open responses gathered in surveys and interviews highlighted that EU-wide adoption of accelerated assessments and rolling review played an important role in fast approval and access to medicinal products for COVID-19. These **EU-level mechanisms prevented duplication of efforts and timely availability of the right expertise**, which particularly benefited smaller MSs with limited capacity and expertise. For example, industry highlighted the EU added value of leveraging and consolidating scientific expertise across EU to provide rapid interactive scientific advice. This promoted use of best methods and study designs for developing COVID-19 medicinal products, thus ensuring the development of high-quality, safe, and effective vaccines for European citizens.

Table 7 provides an overview of the authorisation dates for several COVID-19 vaccines that were approved to tackle the pandemic in the EU, and compares it with the authorisation dates in the USA and Japan.

Table 7 Comparison of authorisation dates for COVID-19 vaccines in the EU, USA and Japan.

COVID-19 vaccine name	EU (conditional marketing authorisation)	USA (Emergency Use Authorisation)	Japan (Special Approval for Emergency)
Comirnaty	21/12/2020	11/12/2020	14/02/2021
Spikevax	06/01/2021	19/12/2020	21/05/2021
Vaxzevria	29/01/2021	n/a	21/05/2021
Jcovden	11/03/2021	27/02/2021	n/a
Nuvaxovid	20/12/2021	n/a	18/04/2021

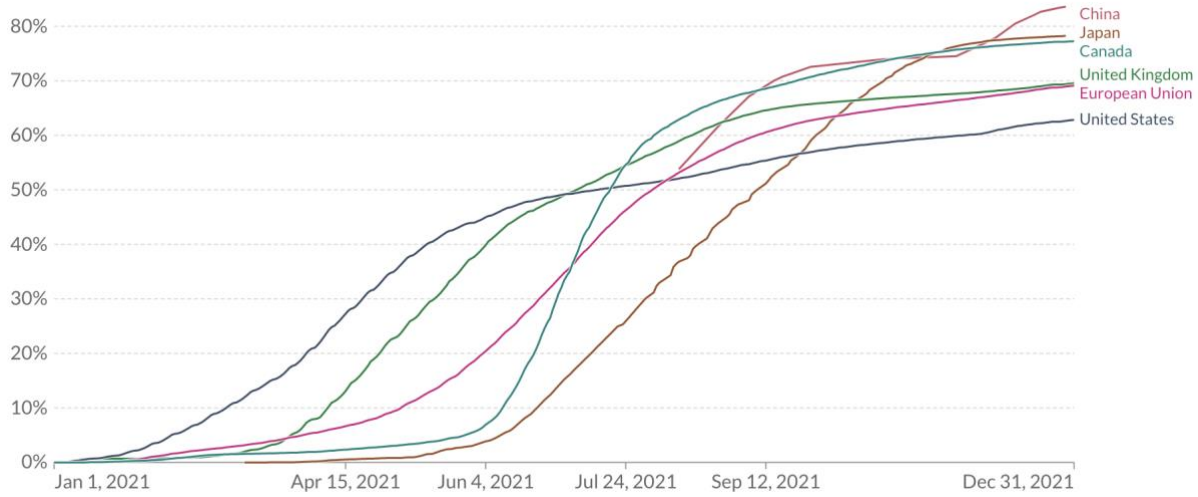
Source: COVID-19 Track Vaccines (COVID19 Vaccine Tracker, n.d.) and EMA (European Medicines Agency, n.d.-c).

While outside the scope of the general pharmaceutical legislation, stakeholders shared the view that the **joint procurement agreement was critical for securing and facilitating equitable access to vaccines** across all MSs. EU-level negotiations with industry helped to establish fair pricing and avoided MSs competing against each other for supplies and driving up prices. It also ensured each MS received vaccines under the same conditions and time. Moreover, the advanced purchase agreement to provide upfront financing for COVID-19 vaccines was a good demonstration of EU added value according to many stakeholders.

A civil society stakeholder mentioned EMA played a central role in **supporting MSs to communicate the risks and benefits of vaccines**. This helped build public confidence in COVID-19 vaccines and

uptake by European citizens (Figure 17). For example, EMA supported regulatory networks to build public trust through various activities such as public stakeholder meetings, media engagement activities and issuing regular pandemic safety updates with accompanying visuals to explain regulatory concepts (Cavaleri et al., 2021).

Figure 17 Total number of people who received all doses prescribed by the initial COVID-19 vaccination protocol, divided by the total population of the country/region, between 1st Jan 2021 and 31st 2021



Source: Our World in Data, 2022

There was consensus across stakeholders that EU-level cooperation was very important for **quick coordinated action to ensure medical supply chains continued to function** during the pandemic. This is important as medical shortages are not limited to one market and cannot be solved at a national level alone. Health services highlighted the EU Executive Steering Group on Shortages of Medicines Caused by Major Events that was an important enabler for the **increased collaboration and data sharing** across MSs to prevent and mitigate supply shortages. Furthermore, EU-level guidelines on the optimal and rational supply of medicines to avoid shortages during the COVID-19 outbreak (2020/C 116 I/01) were cited as being valuable to MSs. These guidelines were important to promote cooperation between MSs, thus preventing stockpiling and encouraging sharing of essential medicines during the pandemic. In particular, green lanes guidelines were seen as instrumental in facilitating cooperation between MSs to prevent shortages across EU according to several stakeholders. Industry stakeholders valued their inclusion in EU-level discussions on serious cross-border health issues which were critical to avoid shortages for patients during the pandemic. Furthermore, EU guidelines for border management measures to protect health and ensure the availability of goods and essential services (2020/C 86 I/01) were cited as valuable in limiting export restrictions and securing free movement of goods across the EU.

4.3 Is the intervention still relevant?

Relevance is the evaluation criterion that explores the relationship between the objectives of an intervention, and thus the provisions of the legislation and actions foreseen within it, and current and anticipated future needs: is the legislation capable of responding to these needs? The main objectives of the legislation are (i) guaranteeing a high level of health protection for the people of Europe, particularly through quick access to innovative and reliable products and increased market surveillance; (ii) ensuring a well-functioning internal EU market in pharmaceutical products in the context of globalisation and encouraging competitiveness of the European pharmaceuticals sector; (iii) respond to challenges presented by the continued enlargement of the European Union; and (iv) improving the overall consistency and visibility of the EU regulatory system through rationalisation and simplification and transparency of procedures and decision-making. Relevance, however does not explore the topic whether the implementation of the legislation in practice has led to positive effects, which was discussed in the section on effectiveness.

Before analysing the links between the current needs and how relevant the legislation is, we need to consider the megatrends that will shape the future of health in Europe. The EU's Joint Research Centre has identified (EC Knowledge for Policy, 2022) the following megatrends relevant to health:

- Acceleration of technological change and hyperconnectivity: this megatrend includes new ways to generate health data at the individual level through personal devices, sensors and tools, often integrated into 'wearables'. These new technologies can support decentralised and virtual clinical trials and generate vast amount of unstructured real-world data. How this translates into evidence through new models and methodologies (including machine learning/artificial intelligence) for regulatory assessment pre- and post-market authorisation has not yet been fully established.

- Emerging infectious diseases require new and innovative approaches as increasing antimicrobial resistance will lead to new epidemics. The COVID-19 pandemic accelerated the arrival of mRNA vaccine technologies, however new classes of antimicrobials will need to be developed against the backdrop of limited commercial incentives.

- Personalised approaches in healthcare will lead to new types of predictive, diagnostic and therapeutic approaches, and solutions will become bespoke and targeted, shifting from the small-molecule blockbuster medicines manufactured large-scale in industrial settings to complex combination products targeting smaller populations sizes.

The objectives of the general pharmaceutical legislation remain valid after 15 years despite the introduction of multiple specialised legislations and several amendments of those. It has responded well to the need to incentivise the development of innovative medicines in Europe and through a globally recognised robust regulatory framework, authorise high quality, safe, and efficacious medicines. It also responded well to the need to continue monitoring the safety of medicines post-authorisation via a centralised pharmacovigilance system and ensuring compliance with rules of marketing, manufacturing and distribution of medicines. This flexible and harmonised system has responded well to the need to make medicines 'available' for EU Member States. In addition, through harmonisation and transparency measures it made the system overall more consistent, an attractive feature in the global context for medicine developers.

However, the legislation has limited provisions, mandate and specific action available to ensure that authorised medicines are launched in all Member States and thus ensure equitable access to those for citizens across the EU. Therefore, the relevance of the legislation to equitable access to medicines is low.

Another but related aspect is affordability of medicines, especially innovative medicines addressing complex diseases often for smaller patient groups, where the legislation has foreseen relevant actions, such as the support for launch of generic medicines without delay after the expiry of regulatory protection period. The legislation is addressing needs with the Bolar provision on the use of research data, however affordability of medicines continues to be a challenge for many EU Member States.

Looking into the future, new objectives would need to be considered for the legislation to remain relevant in the face of the megatrends. This includes the readiness and adaptability of the legislation to respond to technological developments and rapidly increasing presence of digitalisation in new tools generating regulatory evidence and medicinal products preventing, diagnosing and targeting diseases. Continued relevance also involves providing targeted incentives to the development of those medicinal products that respond to high unmet medical needs, for example for therapies against antimicrobial resistant infections.

The recognition of the increasingly complex and advanced therapies as medicinal products within the legislation is also important to ensure continued relevance of the legislation to permit authorisation of those products in a streamlined manner for all manufacturers, small to large, commercial or otherwise.

4.3.1 The extent to which the general pharmaceutical legislation responded to the needs and problems

Changes to the general pharmaceutical legislation in 2004 were rooted in the core principles of enabling 'free movement of goods' and 'protection of public health' (Hartmann & Hartmann-Vareilles, 2005) through a number of specific actions. Data on the extent to which the needs and problems have been addressed are shown in the effectiveness section.

The general pharmaceutical legislation has established a robust and flexible authorisation system for medicines which includes the centralised procedure and national authorisation procedures via the MRP/DCP. This framework ensures availability of high quality, safe and efficacious medicinal products in Europe. However, the EU legislation provides few provisions that would tackle access to medicines and thus it responded overall less well to the need of guaranteeing high-level of public health in Europe.

Stakeholders acknowledged that accelerated assessment and conditional marketing authorisation provide necessary mechanisms for promoting early access to medicines for patients. However, products recommended for authorisation by the EMA are not actually accessible in all EU markets, particularly in smaller Member States. It should be noted that provision of healthcare is the responsibility of individual Member States, including pricing and reimbursement decisions. Therefore, access to medicines remains a complex challenge and depends on many factors, including pharmaceutical companies' market launch decisions, the result of additional relative cost effectiveness assessment, and affordability for patients and national health systems. In summary, the general pharmaceutical legislation has limited relevance regarding ensuring access to medicines in Europe.

The legislation has direct relevance to and responded well to the need of approving innovative medicines in Europe. According to public authority stakeholders, the legislation has a "fairly wide scope that is adaptable and can deal with new products through guidelines". This view was also shared by several industry stakeholders. However, academics and civil society organisations noted that in certain areas, such as nanomedicine and medical devices, the legislation has not responded as well.

Medicine shortage has been recognised as an important problem in Europe and the legislation has direct relevance to identifying and acting on shortages through obligation for MAHs to keep sufficient stocks of medicinal products and report potential future shortages. Nevertheless, civil society and healthcare professionals felt that the problem is not adequately addressed in the current legislation.

Within the survey, stakeholders identified areas where the current legislation has addressed stakeholder needs to the greatest and least extent. Some of these areas are listed in the table below:

Table 8 Extent to which the current legislation has addressed stakeholder needs (survey analysis)

Stakeholder type	Areas addressed to the greatest extent	Areas addressed to the least extent
Industry	Investment in new therapies facilitated by regulatory data protection Development, manufacture and access to biosimilars Development of new medicines and their authorisation (including ATMPs and PDMPs) Access in all member states to high quality medical products GMP requirements for ATMPs Conditional marketing authorisations and additional data protection for a new indication Parallel distribution and parallel import for CAPs and NAPs	Availability of digital information (SmPC, labelling etc) Pharmacovigilance roles and responsibilities – overlapping scope of responsibilities at EU and MS levels Vaccines: development pathways (require accelerated pathway as standard), access (equal across MS) and the supply chain Lack of clear EU regulation on digital information and advertisement Role of EMA in combination products Incentives for manufacturing in EU as opposed to development Harmonisation and usability of IT infrastructure and digital systems – too complex and time-consuming Lack of centralised procedure for clinical trials and their non-interaction with relevant GMO legislation which prevents clinical trials of investigational gene therapies

		Specific recognition of wholesalers in the legislation Hospital exemptions and their differential interpretation in MSs – creates different safety standards Simplification of packaging and licensing to support free movement of medicines Value added medicines – no legal definition and common regulatory pathway
Civil Society organisations representing patients and consumers	Strengthening pharmacovigilance – ability to report side-effects directly Safety and quality of medicinal products Security of supply Antimicrobial resistance ATMPs and their categorisation	Post authorisation safety and efficacy studies Pharmaceutical pollution which leaves too much to the member states Legislation around biosimilars which states they are a priority but does not encourage their use Insufficient measures to ensure availability throughout the EU IP incentives which are too open to abuse without sufficient safeguards Affordability (or measures for) are not sufficiently enforced and current mechanisms allow very high prices. Lack of conditions attached to public funding and transparency
Public Authorities	Quality of medicines - safety and effectiveness ensured via central authorisation Harmonised system for marketing authorisation reducing workload and ensuring smooth processes Transparency around authorisation Bringing new medicines to market Security of supply	Ensuring high quality comparative trial data pre-authorisation suitable for HTA Medicine shortages Access to medicines in smaller member states; affordability Therapeutic radiopharmaceuticals: inconsistent/non-applicable legislations Insufficient EU level support on coordination of data post-marketing authorisation Fee regulations – no longer meeting NCA needs Keeping pace with developments in science and technology - New manufacturing technologies in GMP guidelines, different applicable frameworks/regulations Harmonisation between member states
Academics	Orphan medicine and innovation Quality of medicinal products	Access and affordability Harmonisation of HTA (clinical evidence) Paediatric medicine development Public input for medicine development Research and innovation by academia and not for profit
Health Services	Ensuring high quality and safety of medicinal products Improved pharmacovigilance	Medicine shortages Accelerated approval pathways – opinion that they are overused Lack of support for NCAs in implementing measures that promote financial viability for wholesalers – endangers timely access

4.3.2 Relevance of the general pharmaceutical legislation's objectives and required actions to current needs and problems and expected developments related to medicinal products in the EU

The general pharmaceutical legislation's objectives continue to remain relevant for the present and the future, particularly the objectives responding to the needs of safeguarding public health in Europe, development and authorisation of innovative medicinal products, and ensuring the safety and quality of medicinal products in the EU.

However, stakeholders added that while the legislation's objectives remain relevant, they need to be adapted to fit additional needs and future developments. For example, affordability has become a main problem especially for innovative products which directly impacts on accessibility of these products and further stifling available budgets for procuring other product categories, including generic medicines. The lack of a common definition of unmet medical needs is creating uncertainty regarding incentives available to develop medicines to meet those needs.

Figure 18 Stakeholder views on relevance of the objectives and required actions of the general pharmaceutical legislation (survey analysis)

How relevant is the current legislation, including its objectives and required actions, with regard to the following aspects?	All stakeholders average score	Individual stakeholders average score					Agreement between stakeholders	Ranked Relevance
		Industry	Civil Society	Public Authorities	Academic	Health Services		
Addressing current needs related to the development and authorisation of medicinal products in the EU	3.4	3.5	2.8	3.5	3.5	3.7	High	most relevant
Adapting to new therapies and their method of administration	3.1	3.4	2.6	3.2	2.9	3.3	High	most relevant
Ensuring the safety and quality of medicinal products	4.2	4.5	3.8	4.3	4.4	4.0	Low	most relevant
Ensuring access to affordable medicinal products for those that need them	2.4	3.0	2.2	2.4	2.0	2.4	Low	least relevant
Maintaining security of supply of medicinal products in the EU	2.9	3.3	2.7	2.9	3.3	2.2	Med	least relevant
Maintaining resilience and responsiveness of health systems during health crises	2.9	3.2	2.8	3.1	2.9	2.4	High	least relevant
Minimising the impact of medicines on the environment through appropriate risk assessment	3.0	3.4	3.2	2.6	3.5	2.4	Low	
Supporting successful digital and scientific transformation to meet the needs of medicinal product development and related technological developments	3.0	2.5	3.0	3.0	3.4	3.3	High	
Promoting the attractiveness of the EU system for developers compared to other jurisdictions	2.9	2.7	2.7	3.1	3.3	2.8	High	

Source: Targeted survey data

Stakeholder consultations covered the issue of relevance to identify areas where the legislation may not have suitable objectives and actions foreseen to address needs from stakeholder perspectives. The findings need to be carefully considered as they may not necessarily mean certain areas are highly important (or not important) or whether the legislation delivered on stakeholder expectations. Misunderstandings about the concept of relevance among responding stakeholders cannot be excluded.

All stakeholders considered that the legislation has the highest relevance to ensuring the safety and quality of medicinal products marketed in Europe. This is a positive aspect as the legislation explicitly set out to address this objective. A related aspect recognised by stakeholders as highly relevant is the legislation responding to needs related to the development and authorisation of medicines.

However, the legislation was rated as of low to moderate relevance to other important aspects. The lowest relevance of the legislation was related to ensuring access to affordable medicines, which implies that in stakeholders' views the legislation had limited ability (provisions and actions) to address this need and meet the declared objective of the legislation. This view was confirmed in interviews with

public authorities, civil society and healthcare professionals as an area where the legislation needs to put more emphasis, although there was acknowledgement that access also falls under national competences to a large extent. In addition, it was pointed out that access to medicines is dependent on affordability which in their view needs to be explicitly addressed in the legislation's objectives.

Related to access is the involvement of HTA bodies, pricing & reimbursement (P&R) authorities and payers in providing access to authorised medicines. While the medicines regulatory authorities (national and EMA) promote access through facilitating the authorisation process, ensuring the quality, safety and efficacy of medicines, HTA bodies, P&R authorities and payers ultimately ensure products are available to those that need them. These organisations make decisions based on cost-effectiveness of medicinal products and national contexts and budgets, meaning very expensive medicines may not be reimbursed unless they are seen to be offering a much higher benefit compared to existing treatments. Such comparative effectiveness data or other relevant data are not always readily available as companies do not need these to obtain marketing authorisations, in particular for innovative medicines from the EMA. Data available for products that obtained CMA is even more limited and poses challenges for national authorities in their assessment. Overall, civil society, national regulators and payers highlighted the need to address this problem and improve timely access to new medicines, especially those authorised through the centralised procedure.

Importantly, stakeholders rated the legislation to be of low relevance to maintaining security of supply of medicines. This is an unanticipated finding as the legislation has two specific provisions to address the supply of medical products in the EU: article 23a for MAHs to provide advanced notification to NCAs about supply interruptions and article 81 for MAHs and wholesalers to ensure appropriate and continued supply to cover the needs of patients. It should be noted that since 2016 the EMA/HMA set up a taskforce to improve continuity of supply and publishes a shortage catalogue. Nevertheless, so far medicine shortages are dealt with at national level by NCAs. Nevertheless, healthcare payers and public authorities expressed in open responses and interviews that security of supply is relevant for the legislation and supply chain disruptions continue to be a major issue across the EU.

At a more granular level, public authorities rated the relevance of the current legislation's environmental risk assessment as low to moderate to minimise the environmental impact of medicines. Industry stakeholders rated the current legislation having low relevance to digitalisation and scientific and technological transformation that are needed for medicine development

Overall, stakeholder groups agreed in interviews that the current legislative framework and obligations need to be adapted in light of scientific and technological developments. These new technologies are giving rise to new types of medicinal products that do not fit in with the existing paradigms of what a medicine is and how it should be evaluated. For example, ATMPs and medicine-device combination products find themselves at the borderline between the general pharmaceutical legislation and other legislations e.g. the ATMP and medical device regulations. Therefore, there is demand from stakeholders (civil society, healthcare professionals, industry and public authorities) for clarity with regard to requirements for borderline and combination products. Real-world evidence, big data and digitalisation have not been accommodated to their full potential according to industry and public authorities. Other areas noted include nanomedicines, microbiome-based products, nuclear medicine; the use of artificial intelligence (AI) and digitalisation are not adequately accommodated by the current legislation.

Current needs and problems not sufficiently recognised in the EU general pharmaceutical legislation include actions countering AMR despite a looming public health crisis of resistant infections. A recent study has shown that there are not enough antibiotics under development within the global clinical pipeline to tackle this threat (Theuretzbacher et al., 2020). Environmental impact of medicines is also a relevant concern within the EU, as residues of pharmaceuticals continue to be detected in the environment (Dusi et al., 2019), not yet tackled via the legislation. However, there are a number of other EU regulations that deal with waste and chemicals that target these needs to a small extent (for more information, see the Coherence section).

Further needs and problems identified through the stakeholder consultation where the current legislation has limited or no relevance include: tracking off-label use of medicines (healthcare professionals and civil society), and more deliberative actions (industry and public authority) concerning the objective of ensuring global attractiveness of the EU.

4.3.3 Lessons learned from the COVID-19 pandemic about the relevance of the general pharmaceutical legislation to health crisis resilience and responsiveness

The COVID-19 pandemic brought several challenges for public health, in particular the problem of evaluating the safety and efficacy of urgently needed medicinal products in very short timelines. In this context, the EU general pharmaceutical legislation has allowed the EMA to coordinate appropriate responses to the COVID-19 crisis. Using rolling reviews (an accelerated procedure for assessing data) and collaborating with other regulatory agencies, the EMA was able to grant conditional marketing authorisation (CMA) to the first vaccine for COVID-19 within 9 months since the start of the pandemic (Cavaleri et al., 2021). This success in significantly reducing the timeline for granting conditional marketing authorisation brings lessons for the future on how more flexible and agile approaches can be applied to the EU's regulatory framework for pharmaceuticals. For example, rolling reviews can be adapted to improve interaction between developers and regulators, with the aim of facilitating the development of medicinal products that are needed in preparation for crises and for other areas, such as unmet medical needs. However, these adapted approaches to regulating pharmaceuticals also bring significant costs to regulatory agencies, as more resources are needed, and new ways of working must be developed and implemented. A pandemic (level 4 crisis, according to EMA's plan for health threats) requires the creation of response and strategy teams, additional operational staff and expert groups such as EMA Task Force and Scientific Advisory Groups.

Stakeholders across all groups identified joint procurement and accelerated approval (via rolling review) of vaccines as the chief mechanisms through which resilience and responsiveness was achieved for the EU during the COVID-19 pandemic. Cooperation between MSs through EU bodies and the EMA's flexibility and adaptability were key enablers allowing a coordinated response. These stakeholder views confirm that the EMA has adapted its governance to respond to the scientific, regulatory and operational challenges which can serve as a blueprint for future emergencies (European Medicines Agency, 2022a). Key lessons from this experience include the realisation that approval of new/innovative medicines could be managed at pace and processes could be streamlined without compromising safety and quality to facilitate faster access to innovative medicines and address UMN. However, academics, civil society and some public authorities strongly emphasised that the rolling review and other approaches for accelerating the authorisation process should not be applied routinely as these may compromise safety and quality of medicines when scaled up and EMA's resource requirements (both human and financial) would be prohibitive.

Academic and industry interviewees were positive about increased collaboration among industry and regulators (especially EMA) during the pandemic to share information on stocks and shortages, to provide scientific advice and to generally expedite the medicine development process. Industry actors were hopeful that virtual audits and inspections that were successfully implemented during the pandemic could be continued in the future to reduce the burden on agencies. They were also positive about the exemption of GMO requirements for vaccine development and suggested similar exemptions could be applied for ATMPs in the future that address public health needs. They also suggested that new designs (e.g. adaptive clinical trials) and simplified processes for clinical trials could be accommodated in routine authorisation procedures. Industry also highlighted the temporary flexibilities to the work of qualified personnel, acceptance of digital versions of documents, and remote inspections and audits were helpful adaptions (HMA et al., 2021). Public stakeholders such as academics, civil society organisations and public authorities however felt that higher level of transparency in both regulatory and procurement decision making was warranted in the public interest.

Overall, stakeholders consulted for this study rated as 'low to moderate' the relevance of the legislation in relation to maintaining resilience and responsiveness of health system during health crisis. Health services stakeholders scored this aspect the lowest, while industry stakeholders the highest. It is without doubt that when answering this question, stakeholders were thinking of the ongoing COVID-19 pandemic and both specific elements of the legislations and in broader sense what the EU institutions collectively achieved. Stakeholder interviews specifically pointed to no discernible restrictions stemming from the legislation during the pandemic response, instead they felt that it provided room for flexibility to adapt processes to suit the reality of the situation. In addition to the already mentioned rolling reviews, other flexibilities were achieved through publication of harmonised guidance (e.g. conducting clinical trials during the pandemic) and temporary derogations from certain obligations e.g. environmental risk assessment (Regulation (EU) 2020/1043 of the European Parliament and of the

Council, 2020) and allowed remote processes for source data verification, audits and monitoring (European Medicines Agency, 2022a).

The pandemic also highlighted factors causing shortages such as the reliance on non-EU API producers according to industry and public authorities. The EMA's extended mandate is an important step forward in addressing some of these factors causing shortages. Applicable since 1st March 2022 (Official Journal of the European Union, 2022), the extension of the mandate assigns the EMA the responsibility to set up a monitoring system for events that can lead to public health crises, such as medicine shortages. The extended mandate also seeks to formalise and improve on the regulatory tools used by EMA to respond to the public health crisis brought by the COVID-19 pandemic, such as speeding up regulatory assessments and clinical trial data evaluation. As such, the EMA's extended mandate responds to the early lessons from the COVID-19 pandemic published by the EU Medicines Regulatory Network (EMRN) (Cavaleri et al., 2021), which have parallels in the lessons emerging from our own study. These included:

- Need for rapid and coordinated feedback to medicine developers and the continued dialogue with industry on issues of interest to developers, such as clinical requirements or resolving bottlenecks to scale-up of production
- Need to support and enable rapid advice and approval of large, well-designed trials, including platform trials, that can provide the robust data needed to support decision making and demonstrate that new or repurposed medicines are safe and effective, whilst also refuting as early as possible those which are ineffective and or unsafe
- The emergence of very rare side effects of thrombosis for some vaccines, showed the importance of risk communication and transparency on emerging issues, explaining uncertainty and preliminary nature of interim results
- The side effects also showed how extensive data collection, analysis and visual risk contextualisation can be delivered across Europe in a short time. Early and proactive investment in developing real-world evidence (by EMA) has allowed rapid safety analysis and risk contextualisation. There is room for improving the type and coordination of health data across the EU and enhancing data analytics.

5 CONCLUSIONS & LESSONS LEARNED

5.1 Conclusions

The general pharmaceutical legislation is a successful EU intervention in the sense that it achieved all four high level objectives to some extent. The objective to ensure quality, safety and efficacy of medicinal products was achieved to the largest extent, while that of ensuring access to medicines was achieved to a limited extent. The objectives of ensuring competitive functioning of the EU internal market and attractiveness in a global context were achieved to a moderate extent. With the needs and problems that the 2004 revisions were addressing still remaining relevant, the objectives of the legislation and its revision also continue to remain relevant for the future.

A robust and flexible authorisation system was developed in Europe taking advantage of harmonised processes through the centralised procedure for innovative medicines requiring pooled European scientific expertise; while decentralised procedures at national level available for smaller companies and generic producers with distinct business models. In addition, post-marketing monitoring and reinforced inspections of manufacturing and distribution created a consistent system along the lifecycle of medicines. These elements contributed strongly to the stated objective of ensuring quality, safety and efficacy of medical products in Europe.

The system includes a predictable incentives framework (8+2 years of regulatory data and market protection period) that has kept Europe an attractive market for medicine developers and allowed innovative medicines to be available to national health systems. However, this does delay market entry of generic products, affecting affordability of medicines and MS health budgets. On the other hand, the Bolar exemption has allowed quicker generic entry, but since the implementation of the exemption varies, the benefits are also variable. The creation of a delineated authorisation pathway for biosimilars in Europe before any other jurisdictions, has made Europe a leader in this space, allowing the launch of biosimilars on the EU market and thereby increasing access for patients, choice for health services and providing cost savings for national health system. Yet, there is room for further improving the uptake of biosimilars across EU member states.

It is important to note however that the availability of innovative medicines does not lead to equitable access to those across Member States, another stated objective of the legislation. In effect, the relevance of the legislation is rather limited with regard to access, as companies make decisions on market launch while national health systems retain clear responsibility over providing their chosen healthcare provision (including medicinal products) to their population and likewise for the decision to pay for those. Nevertheless, the legislation was not able to steer market launch decisions of companies and access to medicines primarily in smaller Member States and those with lower per capita healthcare budgets. Access thus remains a real problem for many to guarantee a high level of public health.

The European pharmaceutical industry sector remains second behind the US even though revenues have increased. Similarly, R&D investment has increased in absolute terms but not as fast as in USA or Japan. The US remains the jurisdiction of choice for filing marketing authorisation applications for new active substances but the EU has the second destination for filing and more substances are being authorised by the EMA less than 1 year after the FDA.

The legislation is well-framed, internally coherent and has clear EU added value. However, external coherence has become a challenge in a changing EU regulatory landscape. Emergence of new technologies and borderline cases (that potentially sit between two or more legislations) cause inconsistencies/uncertainties such as the coverage of GMO requirements, environmental challenges and new manufacturing methods along with definition of products e.g. ATMPs, radiopharmaceuticals and medical devices.

Overall efficiency was challenging to assess quantitatively. Most stakeholders were unable to provide quantitative estimates of the costs and benefits associated with the 2004 revision. Where available, data were scarce and many of the relevant data were also not available in literature. There were cost savings associated with harmonisation and streamlining of procedures (for industry and NCAs) and through switch to a single MA renewal after 5 years. Age-standardised mortality rates have improved in all EU countries in the period since 2007 (Santos et al., 2020), albeit with significant variations in improvements across member states and the regulatory system will have been an important contributor, by driving innovation in new medicines as well as ensuring the safety, quality and efficacy of medicines.

Based on additional products coming on the market and EU sales, we have estimated that the 2004 revisions were associated with an additional 170,000-210,000 QALYs across the evaluation period, (based on a median ICER of €33k / QALY) and total additional public health benefits monetised at €4.8bn-€17.2bn. With the upper bound of additional costs estimated at €1.8bn, the 2004 revisions have delivered a positive overall social return.

5.2 Lessons learned

The objectives of the general pharmaceutical legislation remain valid after 15 years. As discussed above, not all objectives have been fully met through the 2004 revision of the legislation and new approaches are needed to address those challenges. However, these are complex issues that the legislation in itself may not be able to solve effectively.

Improved coherence with other specialised health legislations is required to remove uncertainty and improve consistency of interpretation. In addition, improved coherence with other wider EU legislations (e.g. GDPR, REACH, IPR) is required to reduce tensions and improve synergies between legislations, increasing the likelihood of impact in terms of public health, environmental sustainability, digitalisation, etc. This will ensure a more systemic fit of the general pharmaceutical legislation in the wider EU policy framework.

Looking into the future, new objectives will need to be considered for the legislation to continue to remain relevant. This includes the readiness and adaptability of the legislation to respond to technological developments, for example, in new manufacturing methods, and rapidly increasing presence of digitalisation in new tools generating (real world) regulatory evidence and medicinal products preventing, diagnosing and targeting diseases. Continued relevance also involves providing targeted incentives to the development of those medicinal products that respond to high unmet medical needs, for example for therapies against antimicrobial resistant infections. The recognition of the increasingly complex and advanced therapies as medicinal products within the legislation is also important to ensure continued relevance of the legislation to permit authorisation of those products in a streamlined manner for all manufacturers, small to large, commercial or otherwise.

Many lessons have been learned from the recent experience of medicine developers and public authorities having acted under the pressure of the ongoing COVID-19 pandemic. It has demonstrated that there is room for flexibility to adapt regulatory processes and accelerate product development and authorisation processes, including use of remote processes for source data verification, virtual audits and monitoring. This would reduce administrative burden on medicine developers and release capacity for regulatory authorities. EMA has also adapted its governance model to respond to the scientific, regulatory and operational challenges which can serve as a blueprint not only for future emergencies but for a more fit for purpose system as safety and efficacy of increasingly complex and advanced therapies will need to be assessed. It is however noted that EMA has limited resources and its expertise and capacity need to be expanded in order to progress complex dossiers at pace and keep up with the US FDA, where relevant, and do so without compromising safety and quality of authorised medicines.

The pandemic also highlighted factors causing shortages such as over-reliance on one single or very few foreign suppliers for some essential APIs. This might be mitigated through diversification of suppliers. Collaboration between industry and regulators (especially EMA) during the pandemic on stocks and shortages, to provide scientific advice and to generally expedite the medicine development process demonstrated that different interests can be usefully aligned. This however needs to happen under public scrutiny and transparency.

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7 ANNEXES

7.1 Annex I. Methodology and analytical models used

This section summarises the methods used for (i) data identification, collection and analysis and (ii) stakeholder consultations.

7.1.1 Data Identification, collection and analysis

Literature Review

Peer-reviewed literature and policy document review was conducted to gather existing knowledge-base and served as a source of facts and figures. We conducted a comprehensive literature review by first defining relevant search terms (Keywords in English, Dutch, German, French and Spanish 2). Abstracts were screened for relevance and for those relevant full text was obtained. For scientific literature (Peer reviewed papers) online databases PubMed and Scopus were utilised. Grey literature (such as government or business reports, policy documents, theses or conference presentations) were identified from the following sources:

- Key EU institutions and agencies such as the European Parliament, the Council, DG SANTE, DG RTD, HaDEA, ECDC and EMA;
- Websites and online repositories of relevant public competent authorities (European and Member State regulators, pricing & reimbursement bodies) and health technology assessment institutions within the scope of this review;
- Google Scholar;
- Wider information sources including industry organisations and patient associations and civil society organisations at EU and Member State level usually as submissions as part of the stakeholder consultation activities.

All full text documents (>550) were catalogued with their meta data (title, year, authors, item type, ISBN, ISSN etc), read and categorised for relevance and then managed using Mendeley where they could be easily identified, accessed and referenced during the writing of subsequent analytical and evaluation reports.

Comparative Legal Analysis

Comparative legal analysis aimed to provide information around whether proposed EU policy options for the revision of the general pharmaceutical legislation have been implemented or are currently being considered for implementation in other jurisdictions. The analysis presented the elements that had been implemented (if any) and the assessment or evaluation data that was available.

Five countries (Japan, Canada, South Korea, Australia, USA) were selected based on the secondary data analysis (Task 2.3) which identified them as relevant markets with developed economies. Two additional countries were included after discussion with the EC; 1) China as the largest market in Asia and a major generic medicine producer and sophisticated regulatory system for the same, 2) Israel where innovative legislative solutions were expected.

Information was collected via a standardised country reporting template and accompanying guidance document that clearly laid out the scope of the review and was approved by the EC prior to commencement of data collection. The template contained the following sections:

- Context and background to the legal framework on human medicinal products in [X]
- Overview and mapping of the institutional set-up in [X]
- Authorisation procedure
- Incentives and obligations to address antimicrobial resistance
- Future proofing: Adapted, agile and predictable regulatory framework for novel products
- Rewards and obligations related to improved access to medicines
- Facilitate generic and biosimilar entry to ensure affordable established therapies
- Notification and monitoring to ensure security of supply / availability measures
- Quality and environmental sustainability
- Resolving competing aims and interests within the legislation
- Bibliography

The template was completed based on substantive in country legal research and a literature review in both English and national languages. They were completed by national legal experts who had a good understanding of the context and legal systems. National experts were briefed on the project, the methodologies and the templates, and afforded the opportunity to ask questions via a group webinar to ensure methodological consistency across all countries.

The templates were supplemented by targeted interviews (

Table 10) with key stakeholders (competent authorities, pharmaceutical industry association, patient association, payers) which were also conducted by the national experts. Potential interviewees were identified, contacted and followed up at least once in order to get an interview (Table 9). In some cases, interviewee's opted to provide written feedback which was accepted and annexed to the report.

Table 9. Interview Schedule.

Country	Contacted/followed up	Interviewed	Written responses
Australia	7	0	1
Canada	17	2	0
China	6	6	0
Israel	4	0	0
Japan	5	5	0
South Korea	4	0	0
USA	13	0	0

Table 10. Indicative Questions for interviewees

Compared with foreign regulatory frameworks, which features of your country's regulation of pharmaceuticals do you consider distinctive/unorthodox (if any)? When were they introduced? Do you consider these to be advantageous? why?

How does your country evidence the performance of your pharmaceutical regulatory framework? What are the reported indicators (if any)? How do you demonstrate an acceptable trade-off between speed of regulatory approval and clinical performance evaluation?

Which foreign regulatory frameworks have the greatest influence on your country's regulation of pharmaceuticals?

What good practices exist in [X] to:

- Support innovation and address unmet medical needs?
- Ensure the prevention of antimicrobial resistance while promoting the development of new products?
- Regulate new products, new technologies in medicinal products as well as new manufacturing processes?
- Promote wide market coverage by marketing authorisation holders and access to medicines for patients?
- Facilitate the entry onto the market of generics and biosimilar medicinal products?
- Ensure the security of the supply and secure the availability for patients?
- Ensure a high level of quality throughout the supply chain in various production settings, and mitigate the environmental impact of the production of medicinal products?

What formal *international* regulatory collaborations do you have in place?

Is there work on-going regarding regulatory agility?

What are the challenges that remain to be addressed by the legal framework of your country? Have some legislative or policy attempts at addressing these issues remained unsuccessful?

What legislative or policy priority changes were required during the COVID-19 pandemic. What were the related lessons learnt? Are these changes going to be sustained in your country?

What is X's vision, strategy or roadmap for pharmaceutical regulatory framework? What are the related timelines?

+ Country-specific questions to explore the innovative legal options in the country identified via desk research and literature review.

Following completion each country report went through several rounds of review and clarification to increase consistency, address gaps and maximise comparability.

Secondary Data Analysis

Secondary data analysis comprised compiling over 50 macro indicators relevant to several policy areas and conducting statistical, econometric and trend analysis within the EU and compared to data from other jurisdictions.

In the first instance indicators were defined. SMART[37] indicators were proposed based on the objectives of the original legislation and the 2020 pharmaceutical strategy. These were verified and matched against data sources during a series of online working sessions and final selection made based on availability of data. There was prioritisation of time series data reaching back to pre 2005 as well as availability across the markets of EU, Switzerland, USA, Canada, Australia, Japan, and Korea.

In total we identified 55 indicators (Table 11 by policy area). The indicators were grouped in seven policy areas to address the policy elements in scope for the study with specific indicators selected to inform the main evaluation criteria of effectiveness, efficiency, coherence, relevance and EU added value of the legislation.

Table 11. Total number of indicators selected by policy area.

Policy Area	Number of Indicators
Industrial and Economic Competitiveness	13 (IEC 1-13) International (1,2,3,4,5,6,) Internal (7,8,9,10) Sector Profitability (11) Other (12,13)
Research and Innovation	9 (RI 1-9) Conversion rates (1,2,3,4,5,6) Public Research Funding (7) Private Investment (8) Innovative Products (9)
Single Market	6 (SM1-6) Shortage (1,2,3,4) Therapeutic Area Competition (5,6)
Accessibility	10 (ACC1-10) Access to approved medicines (1,2,3) Time to coverage (4,5,6,7,8,9,10)
Affordability	6 (AFF 1-6)
Efficiency	3 (EFF 1-3)
Manufacturing	3 (M1-3)
AMR	3 (AMR1-3)
Environmental	2 (E1-2) Residues (1) Manufacturing Emissions (2)

The indicators were populated using 24 existing proprietary or public databases or sources as listed in Table 12. While each specific indicator must be treated individually depending on completion, coverage, data type and presence of time series element, analysis was conducted to the following plan wherever

[37] Specific Measurable Achievable Relevant Timebound

data allowed and as appropriate. Statistical tests were not applied where the relevant observations were less than 30.

Presentation of longitudinal data covering the period 2000-2020 with stratification where appropriate (e.g. along therapeutic area, indication, product type, company size, legal basis of applications, approval pathway etc).

Comparison of pre and post legislation periods using parametric (Welch's t-test) or non-parametric (Mann Whitney U test) tests for significance between the pre and post periods.

Difference-in-differences estimation by comparing the evolution of the EU 'treated' countries relative to other similar but 'untreated' countries, before and after the 2004 revision of the general pharmaceutical legislation.

Presentation and descriptive analysis of reference groups in other jurisdictions (Japan, US, Switzerland) with statistical comparison wherever possible.

Table 12. List of secondary data sources.

#	Data Source
1	Belkhir et al. Carbon footprint of the global pharmaceutical industry and relative impact of its major players. Journal of Cleaner Production (2019)
2	Drugs@FDA
3	EFPIA
4	EFPIA Report on Key Trade Data Points on the EU27 Pharmaceutical Supply Chain based on Eurostat
5	EU Industrial R&D Investment Scoreboard
6	EU Shortages Database
7	EudraGMDP/GMP/Sites
8	Eurostat /Eurostat Healthcare expenditure statistics
9	IFPMA
10	Informa Biomedtracker
11	Informa Datamonitor Healthcare
12	Informa in-house dataset collected from 20 major funding bodies including Horizon 2020
13	Informa Outlook 2019
14	Informa Pharmaprojects
15	Informa Sitetrove
16	Informa Trialtrove,
17	IQVIA MIDAS sales/sales volume data
18	OECD Health statistics/STAN Database
19	Publicly available trade/economics ministry data
20	Statista
21	Umwelt Bundesamt Database "Pharmaceuticals in the environment", including substances on the European Watch List.
22	US Bureau of Labour Statistics
23	Utrecht University MAA database
24	WHO Health Expenditure

Detailed methodology per indicator along with results of the analysis can be found in the Analytical Report.

Case Studies

Case studies were developed focused on specific issues to illustrate linkages and mechanisms behind trends observed in the data. Note, the Case Study Report do not form part of the present Evaluation Report.

Alongside ongoing data identification, collection and analysis the 'focus areas' of each case study were agreed with the European Commission. The final selection and structure were based upon feasibility criteria (potential to showcase legislative contribution, researchable) and linkage to objectives of policy revisions and intervention logic. The seven case study topics were: 1. Antimicrobial resistance (AMR), 2. Agile/adaptive regulatory systems, 3. SMEs/Regulatory support, 4. Improved access, 5. Affordable generics, 6. Emerging manufacturing and 7. Unmet Medical Need.

Within the scope of and specific to each case study, we conducted a search of the literature. 1) defining relevant search terms, 2) defining relevant data sources, 3) defining relevant time period, 4) screening and selection of relevant papers, 5) snowballing. For scientific literature online databases PubMed and Scopus were utilised, while for grey literature online search engines (e.g. Google) and databases (e.g. Google Scholar, Policy Commons, Overton) were used along with websites of relevant international organisations (e.g. EMA, EFPIA, International society of pharmaceutical engineering, European Association of Hospital Pharmacists, etc) being screened. Additional sources identified on selected and screened sources were also included where relevant. The documents were analysed and information was put under topic headers to structure the data (different for each case study).

Where relevant and applicable, quantitative analysis of secondary data was undertaken specific to the case study to which it applied. Where this has occurred, methods are provided in detail in the individual case studies.

An overall case study format was proposed based around key research questions and sub questions and is presented below:

Summary
Retrospective view

- 1: Nature and extent of the problem
- 2: Objectives of the 2004 regulation
- 3: Evaluation of the achievements of the regulation

Forward looking view

- 1: Evolution of the problem and residual challenges
- 2: Enhanced policy options
- 3: Potential impacts of the revisions
- 4: Synergies and interplay

Key conclusions
Case study references and data sources

In the case of case study 3. SMEs/Regulatory Support there were substantial knowledge gaps and key information interviews were used to address these. We used semi- structured interviews (Table 13) with representatives of 5 leading industry associations to address knowledge gaps that are not covered by the higher levels of evidence. Interviews were performed with relevant stakeholders. Notes were taken and sent back to the interview respondents for validation. The interview notes were analysed and collated in the same way as the documents and referenced in the case study.

Table 13. Interview Protocol for SMEs.

Specific for SMEs…	What goes well at the moment?	What can/ should be improved?	Suggestions for improvement?
Innovation ecosystem (drug discovery and development): • resources (capital, human, etc.) • risks • collaborations (relationship w/large companies, knowledge institutes) • IPR			
Pre-marketing phase: • Regulatory advice, dialogue and training (early-stage SME/ITF Brief Meetings on marketing authorization filing, strategies, orphan drug designation applications, PIPs, scientific advice, etc.) • Scientific advice and protocol assistance (vs. other sources of information; satisfaction; and reasons for asking for advice) • Financial support (financial incentives (fee reductions) in regulatory process; other incentives for SME innovation) • General on: European versus National (CP/MRP/DCP); GMP/GLP; Clinical Trial Directive			
Regulatory approval and requirements: • clinical • non-clinical • manufacturing			
Post-approval management (e.g. fee incentives, advice): • label • pharmacovigilance • HTA			

7.1.2 Stakeholder Consultation: Primary Data Collection

Feedback for the consultation on the Roadmap/Inception Impact Assessment

The Roadmap /Inception Impact Assessment was developed by the EC to inform stakeholders and gather feedback on the possible actions at EU level. The study team received an excel file containing 173 answers (feedbacks) to the published Roadmap/Inception impact assessment along with the 86 attachments in PDF format. The answers were translated from other languages to English, the data was checked for duplicates and campaigns were identified using both Excel and manual checking. When respondents did not use open text answers, the attached PDF documents were consulted in detail. The analysis of the answers was based on a set of topics developed after an initial assessment of all submissions. Using Excel and Word, manual cross-checks of all answers were completed, recording topics and sub-topics as well as the number of times they were mentioned.

A factual summary report in English was produced. This comprises a succinct 5-page report, profiling the participants, highlights of the main topics raised overall and by stakeholder groups, following the elements as set out in the technical specifications.

Open Public Consultation

A survey questionnaire developed in English and agreed with the EC was conducted electronically and it was published on the Commission's 'Have your say' web portal in all European languages for 12 weeks, from 28 September to 21 December 2021 – along with information materials.

The survey had two main topics and several sub-topics (bulleted in Table 14) and served to determine the balance of opinion (overall, and by stakeholder group) on the relative importance of a given issue. The OPC was a mixture of open and closed questions and utilised skip codes to guide participants through the relevant questions depending on their self-categorisation into stakeholder group. There were no character limits imposed on open answers.

Table 14. OPC survey structure.

Backward-looking questions

- Other issues to be addressed in this revision
- Positive and unintended effects of the legislation

Forward-looking questions

- Unmet medical needs
- Incentives for innovation
- Antimicrobial resistance
- Future proofing: adapted, agile and predictable regulatory framework for novel products
- Rewards and obligation related to improved access to medicines
- Enhance the competitive functioning of the market to ensure affordable medicines
- Repurposing of medicines
- Security and supply of medicines
- Quality and manufacturing
- Environmental challenges

It was anticipated that around 500 responses would be received and in total 478 responses were actually received – shown below -by stakeholder group.

Table 15. Number of OPC Responses by stakeholder group**.**

Stakeholder	Responses Received
Industry	179
Public Authorities	37
Health Service Providers	85
Academic	39
Civil Society Organisations and Citizens	106
Other	32
Total	**478**

All 478 responses were downloaded from the EU Survey portal, translated into English, checked for duplicates and campaigns were identified, using a combination of Excel, statistical software STATA and manual checking. The study team conducted quantitative statistical analysis of closed answers and qualitative analysis of the answers provided in text form. All answers provided in text form (over 4,000 entries across 14 questions) were manually checked and emerging themes for each question were reported in a descriptive narrative for each stakeholder group.

A factual summary report in English, comprising of a succinct 8-page report, was produced. An in-depth analysis report was also produced with more profiling of participants, campaign identification and detailed analysis of stakeholder views on the two main topics of the OPC as well as summary of the position papers submitted in PDF format.

Targeted Survey (Survey Report)

Targeted surveys with key stakeholder groups through an online questionnaire were designed to obtain facts and figures – as well as opinions – on the relevance, efficiency, costs and benefits of the current legislation and the scale of anticipated positive or negative impacts of potential new policy elements.

A survey tool was developed and signed off by the EC. The survey had several modules (bulleted in Table 16 below) and incorporated skip codes such that different stakeholder groups were automatically navigated through the questions appropriate for them. All questions were optional and could be skipped or answered with don't know.

Table 16. Targeted Survey Structure.

- Survey explanation (purpose, privacy, scope, time, instructions)
- About you/your organisation (Organisation name, type, participant name)
- Functioning of the legislation since 2005 (effectiveness, relevance, coherence, value add)
- To what extent has the legislation been effective/relevant/coherent/added value with respect to objectives
- Where has the legislation been most/least effective/relevant/coherent/added value
- Provision of supporting evidence or data
- Efficiency (costs and benefits and explanations of answers)
- Elements of future policy options (incentives UMN, AMR, Futureproofing, Access, Competitive Market Functioning, Manufacturing Quality and Environment, Security of Supply, Streamlining)
- Please rate the impact of the following measures on UMN, AMR, Futureproofing, Access, Competitive Market Functioning, Manufacturing Quality and Environment, Security of Supply, Streamlining
- Further comments on your answers above
- Conclusion (the greatest impacts with supporting data)
  Close (invitation to be contacted with follow up questions)

The questionnaire was delivered electronically using the tool 'Survey Monkey' and 220 participants were directly invited. Invites were sent as individual links were possible to enable tracking of participation and were supported by a letter from the EC endorsing the survey. The EC also shared the survey link within relevant networks of public authorities. Of the total number of invitations, over 90 invitations were send to 'intermediary' organisations who were asked to disseminate the survey link through their networks (e.g civil society or association members) in order to snowball the sample further. The survey targeted five main stakeholder groups (industry, public authorities, health service providers, academic and civil society) and had agreed participant targets that were considered suitably representative. The survey remained open for just under 15 weeks between the dates 16th November 2021 and 14th January 2022, and invited participants were followed up multiple times in this period to try and boost participation. The number of individuals and intermediaries invited is shown in Table 17.

Table 17. Targets and invited participants per stakeholder group.

Stakeholder	Targeted	Invited (intermediary)
Industry	65	63 (38)
Public Authorities	50	15 (6)
Health Service Providers	20	40 (33)
Academic	20	63 (7)
Civil Society Organisations	45	39 (11)
Total	**200**	**220 (95)**

Upon closing the survey, data was downloaded to an excel spreadsheet and imported to STATA. Data was cleaned extensively in STATA with suspected duplicate, test, empty and "nonsense" entries exported in full to excel. Within excel the responses were manually reviewed and decisions taken and recorded on their inclusion. In one case two entries from a single person were combined, where the survey had been completed in two separate and distinct parts. One person submitted an amendment to their responses by email which was enacted into the data set. Two people's data sent by email were manually entered into the data collection tool by the evaluation team and then downloaded with the rest of the data. Having received and downloaded 440 entries to the survey, 209 responses remained for analysis after data cleaning.

The process of identification of campaigns was conducted using a combination of statistical software and manual checking in excel according to the following process:

- Identifying responses that matched on all of the 46 closed questions
- Identifying responses that matched identically on any one of the open questions
- Identifying responses that matched to a score of 94% of characters on any one of the open questions using the function 'matchit' in STATA using the "bigram" option for fuzzy logic
- Exporting all potential campaign respondents to excel where they were manually grouped
- Any that could not be assigned to a campaign were decategorized and considered independent entries.

Campaigns of ten or more responses matched by any of the three methodologies were considered for further analysis and separate presentation of the key points from open questions. In accordance with the guidance received on the use of data for campaigns one copy of the campaign response was selected per stakeholder group from blocks of matching closed question answers while others were disregarded from any quantitative presentation.

Quantitative analysis focussed on the tabulation and description of the closed questions where in each case the questions were asked with a 5-point scaled response. There was always a 'don't know' option and respondents also had the option to skip any question. The responses were divided into 5 different stakeholder group to which they had self-categorised: i) Industry ii) Civil Society iii) Public Authorities iv) Academic v) Health Services.

Answers were first tabulated as frequencies of each response per question and stakeholder and then individually attributed a score (1 -5) and these scores were tabulated along with the 'don't know' and 'skipped' options. Following this for each question an average score was calculated per stakeholder. These were then normalised into an "all stakeholder score" which weighted each stakeholder group's score equally and accounted for the different participation rates. Within each subcategory the different aspects were ranked to identify overall which were considered the most/least effective, relevant etc. The average scores were mapped back to the original categories through assignment to five evenly sized groups with 3 at the centre so <1.8 was very small/not at all, 1.8-2.59 was small/slightly, 2.6-3.39 was moderate/moderately, 3.4-4.19 was large/largely >=4.2=very large/extremely.

Agreement between stakeholders was assessed using ANOVA. Agreement between stakeholders was classified as high, medium, and low where $p<0.05$ combined with an F score greater than 4 was considered low agreement with strong evidence that stakeholders did not have consensus between them – inter-stakeholder consensus. Medium agreement was assumed where the P value was <0.06 and the F score was above 3. Those with medium and low inter-stakeholder consensus were further explored using Tukey's test for multiple comparisons to identify the divergent stakeholders.

Finally, the standard deviation was calculated per question and per stakeholder and utilised as an indicator of within (intra) stakeholder consensus. A higher standard deviation signalled less intra-

stakeholder agreement with those above 1.1 being classified as low agreement and below 0.7 high agreement. Where intra-stakeholder consensus was low and sample size permitted these differences were explored related to geographical area of respondent (public health authorities) and subcategory of the stakeholder group (Industry, public health authority, academic).

Open questions were analysed qualitatively. Data was outputted to Excel where questions were allocated to Effectiveness, Relevance, Coherence, Efficiency (retrospective) or to policy blocks (anticipated impacts) and then coded into deductive themes. This data was analysed and summarised integrated with interview and open public consultation data.

Interviews

Semi-structured interviews supported our qualitative and in-depth explorations of the functioning of the current legislation. They also gathered feedback and input on the initial policy elements described in the Inception Impact Assessment, as seen from the perspective of the key stakeholder groups, across the EU member states.

Candidate interviewees were identified by a range of methods (drawing on the study team's knowledge of the sector and preliminary desk research, expression of interest via the targeted survey, Pharmaceutical Committee workshops, recommendation by other interviewees) and the list was verified and inputted to by the EC. Participants met simple selection criteria: senior figures with good knowledge of the legislation either as individual experts or as senior representatives of organisations with a mandate that encompasses the legislation. Interviews targeted participants across all the identified stakeholder group.

Interviews were conducted according to a topic guide enabling them to be loosely structured. Individual questions were tailored to each interviewee. The topic guide was designed in two parts with the first covering the evaluation criteria while the second part of the discussed the problem analysis, policy options and comparison of the policy options.

Interviews were conducted remotely via Zoom or Teams by a team of ten consultants over the period 7th December 2021 and 26th January 2022. A shortened version of the topic guide was shared ahead of the interview. Interviews were an hour and half long and were recorded (with permission) and an auto-transcription created and stored. On some occasions interviews were conducted in groups with multiple participants and organisations in attendance (Table 18 shows interviews as groups and individuals). Following completion of the interviews, summary notes were written up and key meta data (participant(s), organisation, stakeholder group) were transcribed onto them.

Table 18. Interviews targeted and conducted by stakeholder group.

Stakeholder	Targeted	Conducted	Individuals
Industry	40	29	57
Public Authorities	35	9	10
Health Service Providers	15	26	45
Academic	15	4	6
Civil Society Organisations	25	16	20
Total	**130**	**84**	**138**

Summary notes were imported into Nvivo, coded thematically according to the 2020 objectives of the revisions and abstracts were exported for synthesis into the reports.

Workshops

Two remote stakeholder workshops with participants from across the stakeholder groups provided opportunity for the community to deliberate on progress and conclusions to date and supplement previous data collection.

Each half day workshop was hosted via zoom and followed the structure of:

- Introduction from the EC
- Plenary presentation including opening slido (interactive poll) from Technopolis Project Lead

- Breakout groups: Brief presentation followed by participatory discussion.
- Plenary presentation from each breakout group
- Closing presentation on next steps and closing slido from Technopolis Project Lead

In both cases a 'save the date' was followed by an invite and a discussion paper on the workshop topics 2 weeks prior to the event. Breakout group topics were provided in advance after agreement with the EC. Participants were able to state a first and second preference for their breakout groups and first choices were facilitated the vast majority of the time. Each breakout group had a facilitator and a presenter (from either Technopolis or a project partner) and a technical support from Technopolis Group. Breakout groups were large and to facilitate participation muting and unmuting of mics was strictly led by the facilitator while participants were also free to use the chatbox continuously and this was tracked and responded to. Observers from the EC were in attendance in all breakout groups. Key details about the workshops are shown in Table 19.

Table 19. Details of the workshops.

	Workshop 1: Evaluation	Workshop 2: Impact Assessment
Date	19th January 2022	25th April 2022
Invited	246	339
Attended	208	199
Retention at final plenary	80%	90%
Breakout Groups	1. Safeguarding Public Health 2. Europe's regulatory Attractiveness 3. Accommodating advances in science and technology 4. Ensuring access to medicines 5. Functioning of the EU market for medicines	1. Enabling innovation including for UMN 2. Ensuring Access to Affordable Medicines for Patients 3. Enhancing the security of supply of medicines and addressing shortages 4. Reducing the regulatory burden and providing a flexible regulatory framework

7.2 Annex II. Evaluation matrix

Evaluation question	Operationalisation / Sub-questions	Judgement Criteria	Indicator (for quantitative indicator abbreviations, see Analytical report)	Analytical approaches (tasks)					
				2.1	2.3	2.4	3.4	3.5	3.6
	Effectiveness								
1. To what extent have the actions envisaged by the general pharmaceutical legislation contributed to achieving the following objectives?	Safeguard public health	For all Effectiveness questions: Degree to which quantitative indicators show positive trend over time and this is corroborated with qualitative information (where available)	RI-9, ACC-1, EFF-2, AMR-1 In addition: adverse reaction data trends (EudraVigilance) Stakeholder view		☐	☐	☐	☐	☐
	An attractive and robust authorisation system for medicines		IEC-2, IEC-4, RI-4, RI-5, ACC-2, EFF-3 Stakeholder view		☐	☐	☐	☐	☐
	Timely patient access to medicines		ACC-3, ACC-4, ACC-8, ACC-9 Stakeholder view		☐	☐		☐	☐
	Minimise inefficiencies and administrative burden of regulatory procedures		ACC-6, EFF-3 Stakeholder view		☐		☐	☐	☐
	Provide harmonised measures for an improved functioning of internal market for medicines		ACC-1 (approval pathway), ACC-6, IEC-7, IEC-8, IEC-10		☐				
	Quality of medicines including through manufacturing rules and manufacturing and supply chain oversight		SM-3, MI-3 Stakeholder view	☐		☐	☐	☐	☐
	An integrated lifecycle model with clear and appropriate responsibilities including post-marketing obligations and oversight		ACC-1 (approval pathways) Expert legal opinion Stakeholder view		☐		☐	☐	☐

Evaluation question	Operationalisation / Sub-questions	Judgement Criteria	Indicator (for quantitative indicator abbreviations, see Analytical report)	Analytical approaches (tasks)					
				2.1	2.3	2.4	3.4	3.5	3.6
	A competitive market for medicines in the EU, including taking into account market effects impacting on affordability		IEC-1, IEC-4, IEC-12, IEC-13, AFF-1, AFF-4, AFF-6, SM-5, SM-6, AMR-1		☐	☐			☐
	Make it easier to place generic/biosimilar products on the market		AFF-4, AFF-5 Stakeholder view		☐		☐	☐	
	Enable innovation for the development of high quality, safe and effective medicines in a way that harnesses the benefits of digitisation and emerging science and technology		AMR-3, AMR-4, RI-1 to RI-4 Number of clinical trials with digital end points, real world data, complex trial design	☐	☐	☐	☐	☐	☐
	Openness to cutting-edge products and integrated therapies		ACC-1 (product type, approval pathway) Stakeholder view		☐	☐	☐	☐	
	Improve competitiveness of EU pharmaceutical industry on the global market		IEC-3, IEC-5, IEC-12, IEC-13, IEC-10	☐	☐				☐
	Enhance the security of supply of medicines and address shortages		SM-1, SM-2, SM-3, MI-1, MI-2 Stakeholder views		☐	☐	☐	☐	
	Reduce the environmental footprint of medicines		EI indicators	☐	☐				
2. How do the achieved results and impacts compare with the expected ones?	To what extent the results of the legislation meet the need of stakeholders?		Use available indicators and contrast with stakeholder view		☐		☐	☐	☐
3. Which were the key contributing and hindering factors in achieving the intended objectives?	To what extent has the type of legislative act, i.e. a Directive, been a contributing or hindering factor in achieving the intended objectives?		Use available indicators and contrast with stakeholder view		☐		☐	☐	☐

Evaluation question	Operationalisation / Sub-questions	Judgement Criteria	Indicator (for quantitative indicator abbreviations, see Analytical report)	Analytical approaches (tasks)					
				2.1	2.3	2.4	3.4	3.5	3.6
	To what extent has Directive 2001/83/EC been transposed by Member States in a way that allows the effective implementation; which are the factors hampering the implementation; to what extent are these factors influenced by regional and national conditions Are there any unexpected or unintended effects that occurred and which drove or hindered progress?		Expert legal opinion Stakeholder view	☐			☐	☐	
4. To what extent is the general pharmaceutical legislation relevant to position the EU regulatory system in an international context, including the attractiveness of the EU system for developers compared to other jurisdictions?	To what extent non-EU based sponsors conduct trials in the EU? To what extent non-EU based sponsors apply for marketing authorisation in the EU?		IEC-4, IEC-6, RI-6 (comparative), EFF-1 (comparative)		☐		☐	☐	
	Efficiency								
5. What have been the main costs (e.g. implementation costs, authorisation costs, life cycle management, staff time etc.) to implement and apply the general pharmaceutical legislation for the different actors concerned (e.g. Commission, Member States, industry, patients, researchers, etc.)? What were the factors driving these costs?	What have been the main costs (per stakeholder category) implications of the legislation?	The implications of the legislation can be monetised in an attributable way	Cost per product development and implementation steps	☐			☐		☐
	What have been the cost drivers?	Views on relevant drivers and their contribution to overall costs	Top cost elements Stakeholder view	☐			☐	☐	☐

Evaluation question	Operationalisation / Sub-questions	Judgement Criteria	Indicator (for quantitative indicator abbreviations, see Analytical report)	Analytical approaches (tasks)					
				2.1	2.3	2.4	3.4	3.5	3.6
6. What social, environmental and economic benefits has the general pharmaceutical legislation achieved for the different stakeholders and what is the corresponding monetised value, where possible and relevant to estimate?	What have been the social benefits of the legislation?	Degree to which quantitative indicators show favourable trend over time and this is corroborated with qualitative information (where available)	AFF-1, AFF-2, AFF-3, AFF-3 In addition: Change in unmet healthcare needs Stakeholder view		☐	☐		☐	
	What have been the economic benefits of the legislation?	Degree to which quantitative indicators lead to favourable trend over time	IEC-7, IEC-8, IEC10 In addition: Foreign direct investment in the pharmaceutical sector		☐				
	What have been the environmental benefits of the legislation?	Degree to which quantitative indicators lead to favourable trend over time	EI-1, EI-2 Residues of pharmaceuticals in the environment and emissions from manufacturing plants	☐	☐				
7. To what extent were the general pharmaceutical legislation's costs proportionate to its benefits (i.e. positive outcomes)?	What is the scale of the significant and monetisable costs and benefits, applying the principle of proportionate analysis? What is the ratio of those significant costs and benefits? What is the balance of those costs and benefits when including non-monetisable aspects?	The extent to which the model result in positive outcomes	Partial cost benefit analysis will consider monetisable costs and benefits and accompanying multi-criteria analysis will assess the balance when including non-monetisable aspects	☐	☐		☐	☐	☐
8. What have been the costs of partially meeting or not meeting some of the objectives and requirements of the general pharmaceutical legislation?	What share of the total costs can be attributed reasonably to each of the specific objectives of the legislation? What is the scale / value of the benefits associated with each	The cost and benefit items can be attributed to objectives and these can be aggregated	Cost-Benefit model will integrate share of costs and value of benefits for each objective and jointly	☐	☐		☐	☐	☐

Evaluation question	Operationalisation / Sub-questions	Judgement Criteria	Indicator (for quantitative indicator abbreviations, see Analytical report)	Analytical approaches (tasks)					
				2.1	2.3	2.4	3.4	3.5	3.6
	specific objective and attributable to the legislation? What have been the total costs of meeting each of these specific objectives, jointly and severally?								
9. Which elements of the general pharmaceutical legislation pose an administrative burden or are overly complex? What are the administrative costs for the different actors? Which provisions could be further simplified?	Which are the burdensome or complex aspects of the legislation?	The degree to which stakeholders can point to attributable administrative burden	Top 5 'burdens' overall and by key stakeholder group	☐			☐		
	What is the level of costs corresponding to these aspects?	The degree to which administrative burden can be quantified by stakeholders	Median value of costs associated with the principal direct costs for each key stakeholder group	☐	☐		☐		
	Relevance								
10. To what extent has the general pharmaceutical legislation responded to the needs and problems concerning medicines identified in section 1.3 for the 2004 revision?	To what extent definition of new therapies and new forms of administration routes enabled innovation?	Degree to which quantitative indicators show favourable trend over time and this is corroborated with qualitative information (where available)	ACC-2, SM-5, SM-6 Stakeholder view		☐		☐	☐	
	To what extent the new pathway for biosimilars responded to the needs?	Degree to which quantitative indicators show favourable trend over time and this is corroborated with qualitative information (where available)	AFF-4, AFF-5, AFF-6 Stakeholder view		☐		☐	☐	
11. To what extent are the general pharmaceutical legislation's objectives and required actions relevant today to address the current	How have the needs and problems identified for the 2004 revision evolved since then?	Degree to which quantitative indicators show identifiable trend over time	RI-5, RI-6, RI-7, RI-8, ACC-1, ACC-2, ACC-5, AFF-1, AFF-2, AFF-3		☐				☐

Evaluation question	Operationalisation / Sub-questions	Judgement Criteria	Indicator (for quantitative indicator abbreviations, see Analytical report)	Analytical approaches (tasks)					
				2.1	2.3	2.4	3.4	3.5	3.6
needs and problems and expected scientific and technological developments related to medicinal products in the EU?	What are the current needs and problems related to the use of medicinal products and how will they evolve (e.g. fulfilling unmet medical need, access to affordable medicines, security of the supply chain, adaptation of the regulatory framework to scientific and technological developments)?	Views on relevant needs and problems corroborating quantitative trends of indicators	Analysis of the current level of indicator available from T2.3 and contrast those with stakeholder view		☐		☐	☐	☐
12. To what extent is the general pharmaceutical legislation relevant to health crises resilience and responsiveness? What are the lessons learned from the COVID-19 pandemic?	To what extent is the general pharmaceutical legislation relevant to health crises resilience and responsiveness?	The degree to which stakeholders and experts can point to relevant examples	Examples of application of the legislation during crises management and response Expert legal opinion Stakeholder view	☐		☐		☐	☐
	What are the lessons learned from the COVID-19 pandemic?	The degree to which stakeholders can articulate learnings	Stakeholder view	☐				☐	☐
	Coherence								
13. To what extent is the general pharmaceutical legislation coherent internally? Have the different elements of the legislation have operated together to achieve all the objectives of the legislation in a coherent way? Which are the reasons for the perceived tensions between innovation, access and affordability and which are the factors influencing them? ***(Internal coherence)***	To what extent is the EU legislation coherent and different elements operate in synergy to achieve all of its objectives? Are there tensions between the objectives linked to innovations, access and affordability of medicines? If yes, what are those? How could these be resolved?	The degree to which (positive or negative) interdependencies of the elements of the general pharmaceutical legislations can be identified and where needed resolved.	Expert legal opinion via: analysis of potential overlaps, contradictions, or other inconsistencies between its provisions/requirements analysis of whether its provisions adequately fulfil its objectives (i.e., safeguard public health and ensure the freedom of movement of these products). Stakeholder view on issues and solutions (especially Member State authorities in charge of the implementation and	☐		☐		☐	☐

Evaluation question	Operationalisation / Sub-questions	Judgement Criteria	Indicator (for quantitative indicator abbreviations, see Analytical report)	Analytical approaches (tasks)					
				2.1	2.3	2.4	3.4	3.5	3.6
			enforcements of this legislation at national level).						
14. The general pharmaceutical legislation has strong links with lex specialis pharmaceutical legislations. To what extent has the general pharmaceutical legislation created an effective and coherent link with the specialised pharmaceutical frameworks that is not hampered by undue complexity? ***(external coherence I)***	Are there overlaps, inconsistencies or ambiguities between the legislation and lex specialis pharmaceutical legislations? Is due to the way the legislation is drafted there is unnecessary complexity in the system? Are there ways the legislations could be better streamlined?	The degree to which interdependencies of the general pharmaceutical legislations and specialised pharmaceutical frameworks can be identified and where needed resolved	Expert legal opinion via: analysis of potential inconsistencies between the general pharmaceutical legislation and the *lex specialis* pharmaceutical laws of core obligations (e.g., authorisation procedures and in-built mechanisms) using a table of comparison and possible legal solutions	☐		☐		☐	☐
15. To which extent is the general pharmaceutical legislation dependent on the implementation of the linked legislation in achieving its objectives? In particular, the link with the non-pharmaceutical legislations and non-pharmaceutical policies should be explored. ***(external coherence II)***	What are the potential links between the pharmaceutical legislation and other EU legislations and policies along the pharmaceutical chain (e.g. development, placing on the market, use, waste management and/or emissions in the environment)? To what extent is the intervention coherent with international obligations? including the SDGs? Are these other legislations (designed at different times with different purpose under different competencies) essential for the pharmaceutical legislation achieve all of its objectives? Do these other legislations hinder the pharmaceutical legislation to achieve any of its objectives?	The degree to which (positive or negative) interdependencies of the general pharmaceutical legislations and other EU legislations can be identified and their effects assessed	Expert legal opinion Note: An in-depth legal analysis is not feasible, however, there is already a vast amount of literature available which would guide the evaluation, meaning a legal analysis would only be needed to debunk or prove a specific inconsistency.	☐				☐	☐

Evaluation question	Operationalisation / Sub-questions	Judgement Criteria	Indicator (for quantitative indicator abbreviations, see Analytical report)	Analytical approaches (tasks)					
				2.1	2.3	2.4	3.4	3.5	3.6
	EU-added value								
16. What has been the added value resulting from the EU intervention in the legislation of pharmaceuticals compared to what could have been achieved at international, national or regional level without such intervention?	What has been the added value of the EU legislation compared to international actions alone? What has been the added value of the EU legislation compared to EU national actions alone? What has been the added value of the EU legislation compared to EU regional actions alone?	The degree to which additional value can be identified as a result of the implementation of the general pharmaceutical legislation	Expert legal opinion Stakeholder view	☐				☐	☐
17. To which extent did the general pharmaceutical legislation strike the right balance between action at EU level and national action? Is it a proportionate response to the problem?	To what extent has the EU legislation been applied in a balanced and proportionate way to problems arising?	The problems and related national/EU actions can be assessed along the same metric/scale and their relationship assessed	Number of MA via the centralised procedure (ACC-1) versus MRP or DCP, ACC-6 Expert legal opinion Stakeholder view	☐	☐			☐	☐
18. What has been the added value resulting from the EU intervention in the context of the COVID crisis (e.g. providing strategic priorities for action, a common framework for action, etc.)?	In what way has the EU intervention added value to the COVID response?	The degree to which added value through quantitative indicators can be attributed to EU action and corroborated by qualitative information for the ongoing crisis	IEC-9 relevant for COVID medicine (therapeutic categorisation) ACC-1 IEC-9 relevant for COVID medicine Stakeholder view	☐	☐	☐		☐	☐
19. To which extent did this EU intervention strike the right balance between action at EU level and national action? Is it a proportionate response to the pandemic?	To what extent has the EU intervened in a balanced and proportionate way with respect to national actions during the COVID crisis?	The degree to which EU actions and national actions can be disentangled	Expert legal opinion Stakeholder view	☐		☐		☐	☐

7.3 Annex III. Overview of benefits and costs

Overview of costs and benefits identified in the evaluation

		Citizens/Consumers		Businesses		Administrations		Society	
		Quantitative	Comment	Quantitative	Comment	Quantitative	Comment	Quantitative	Comment
Costs and Benefits of 2004 revision of Pharmaceutical Legislation (millions of Euro)									
Direct costs									
Direct Compliance costs (adjustment costs)	**one-off**			€250m	Additional investments in IT systems to cope with expanded data requirements on safety and manufacturing, estimated at 0.1-1% of sales. Using the 0.5% median value gives a gross figure of €750m for the EU industry overall. However, the new iT systems have provided wider benefits / productivity gains, so the attributable cost is assumed to be lower (1/3 of gross costs)				
Direct compliance costs (adjustment costs)	**recurrent**			€50m-€100m p.a., €750m-€1,500m in total	Higher costs due to data requirements for new and current marketing authorisations; additional costs for legal departments				
Enforcement costs: (costs associated with activities linked to the implementation of an initiative such as monitoring, inspections and adjudication/litigation)	**recurrent**					EMA: €2.5m-€3.1m p.a., NCAs: €8m-€25m p.a.	Higher staff and evaluation costs for EMA; higher inspection costs for national competent authorities		
Direct benefits									

		Citizens/Consumers		Businesses		Administrations		Society	
		Quantitative	Comment	Quantitative	Comment	Quantitative	Comment	Quantitative	Comment
Health impacts	**recurrent**	25-30 new innovative medicines, in total; producing 170,000-210,000 QALYs in total; which amounts to €4.8bn-€17.2bn in monetised benefits, using WHO guidelines on valuing QALYs	The additional number of new products has been estimated based on a comparison between EMA and FDA authorisations over time; the QALYs are based on estimated average EU income and a median ICER						
Compliance costs: lower costs marketing authorisations	**recurrent**			CP: €4.8m p.a., DCP: €36m p.a.	Cost savings due to the harmonisation and streamlining of procedures associated with the introduction of the DCP and the substantial reduction in the use of the mutual recognition procedure				
Compliance costs: Lower costs marketing authorisations (lower regulatory costs)	**recurrent**			€23m p.a.	MA holders benefited from the switch to a single renewal of a MA 5 years after the original notice of authorisation, eliminating the need for further renewals at 5-yearly cycles, and removing the need for renewals by generics companies				
Enforcement	**recurrent**					€20m-€40m pa	Cost savings for national competent authorities due to streamlining /		

		Citizens/Consumers		Businesses		Administrations		Society	
		Quantitative	Comment	Quantitative	Comment	Quantitative	Comment	Quantitative	Comment
							harmonisation of national authorisation procedures (switch to DCP away from MRP)		
Environmental damage	**recurrent**							0	The 2004 revision has not contributed to reducing the environmental footprint.

Simplification and burden reduction (savings already achieved)

	Citizens/Consumers/Workers		Businesses		Administrations		Society	
	Quantitative	Comment	Quantitative	Comment	Quantitative	Comment	Quantitative	Comment
Title[38]*: (i) direct compliance cost savings (for example adjustment cost savings, administrative cost savings, savings from regulatory charges)*								
Recurrent savings (MAHs)			CP: €4.8m p.a., DCP: €36m p.a.	Cost savings due to the harmonisation and streamlining of procedures associated with the introduction of the DCP and the substantial reduction in the use of the mutual				

[38] Each simplification/saving should be included on a separate line.

				recognition procedure				
Recurrent savings (MAHs)			€23m p.a.	MA holders benefited from the switch to a single renewal of a MA 5 years after the original notice of authorisation, eliminating the need for further renewals at 5-yearly cycles, and removing the need for renewals by generics companies				
Recurrent savings (enforcement)					€20m-€40m pa	Cost savings for national competent authorities due to streamlining / harmonisation of national authorisation procedures (switch to DCP away from MRP)		

PART II: <u>Potential</u> simplification and burden reduction (savings) *Identify further potential simplification and savings **that could be achieved** with a view to make the initiative more effective and efficient without prejudice to its policy objectives[39].*								
	Citizens/Consumers/Workers		Businesses		Administrations		[Other…] _ specify	
	Quantitative	Comment	Quantitative	Comment	Quantitative	Comment	Quantitative	Comment
Description: Our evaluation consultations revealed widespread concerns across industry and regulators about the under-exploitation of digitalisation within the EU pharma regulatory system and the related problem of duplicative activity. As such, there may be areas where further harmonisation and digitalisation of regulatory processes could deliver savings, however, these are contingent on future revisions and operational enhancements being implemented. As an aside, we note that the EMA strategy indicates there are >80 people working on digital transformation and its annual financial accounts show it is investing €5m-€15m a year in new ICT systems. The wider literature on ICT productivity suggests that a 10% increase in ICT investment should produce a productivity gain of around 0.6%[40]								
Recurrent (MAHs)			€9.6m p.a.	There are opportunities for substantial further digitalisation across the EU pharma regulatory system to increase efficiency and duplicative activity				
Recurrent (EMA)					€2.1m p.a.	There are opportunities for substantial further digitalisation across the EU pharma regulatory system to increase efficiency and		

[39] This assessment is without prejudice to a possible future Impact Assessment.

[40] https://www.sciencedirect.com/science/article/abs/pii/S0167624513000036

						duplicative activity		
Recurrent (NCAs)					€12m p.a.	There are opportunities for substantial further digitalisation across the EU pharma regulatory system to increase efficiency and duplicative activity		

7.4 Annex IV. Coherence analysis

Coherence analysis is based on:

- Desk research and a literature review covering, inter alia, evaluation and impact assessment reports of other EU legislation and policies with relevant interface/links with the EU general pharmaceutical legislation.
- Legal analysis by Milieu legal staff together with the support of a senior legal expert Kathy Liddell.
- Stakeholder feedback from the different consultation streams.
- Feedback from representatives of the European Commission in charge of the other EU legislation and policies covered under this analysis.

Five main aspects of coherence are covered under this analysis:

- Internal coherence of the EU general pharmaceutical legislation
- The coherence of the EU general pharmaceutical legislation with specialised pharmaceutical legislation
- The coherence of the EU general pharmaceutical legislation with other EU health legislation
- The coherence of the EU general pharmaceutical legislation with non-health related EU legislation
- The coherence of the EU general pharmaceutical legislation with other EU policies

The analysis of the coherence of the EU general pharmaceutical legislation with other EU legislation and policies entails assessing, inter alia, whether there is some concern of coherence:

- related to their objectives and scope,
- when implemented (e.g., lack of coordination between competent authorities)
- linked to potential overlaps leading to double regulation,
- related to the need to further develop synergies between the EU pharma legislation and other EU interventions.
- due to limited in-built mechanisms to ensure adequate articulation between the EU pharma legislation and other EU interventions.

Overall, more than 30 other EU interventions (EU legislation and policies) have been assessed for the analysis of external coherence. The findings below focus on the EU interventions where potential issues of coherence were identified.

Table 20 Coherence of the general pharmaceutical legislation (survey analysis)

How coherent is the general pharmaceutical legislation regarding the following aspects?	All stakeholders average score	Individual stakeholders average score					Agreement between stakeholders	Ranked Coherance (Industry and Public Authoriteis only)
		Industry	Civil Society	Public Authorities	Academic	Health Services		
All elements of the legislation operating synergistically to achieve optimal results	3.0	3.43	2.8	3.0	2.57	3.3	Low	
Linking with specialised pharmaceutical legislations (e.g. advanced therapy medicinal products, medicines for children and medicines for rare diseases)	3.1	3.2	2.5	3.2	3.1	3.38	High	
Complementing EU health-related legislations on EMA fees	3.0	3.3		2.7			Low	
Complementing EU health-related legislations on Supplementary protection certificates	3.2	3.5		2.9			Low	most coherent
Complementing EU health-related legislations on Blood, cells and tissues	3.1	3.2		3.0			High	
Complementing EU health-related legislations on Clinical trials	3.4	3.39		3.3			High	most coherent
Complementing EU health-related legislations on Medical devices and in-vitro diagnostics	2.8	2.63		3.0			Low	
Complementing EU health-related legislations on Genetically modified organisms	2.2	1.79		2.7			Low	least coherent
Complementing other EU legislations and policies on Data protection (e.g. GDPR)	2.8	2.9		2.8			High	
Complementing other EU legislations and policies on Digitalisation (e.g. Digital Single Market)	3.0	2.57		2.7	3.7		High	least coherent
Complementing other EU legislations and policies on Intellectual Property	3.5	3.4		3.1	4.0		High	most coherent
Complementing other EU legislations and policies on Environment (e.g. REACH, industrial emissions)	2.59	2.9		2.4	2.5		High	least coherent
Sustainable Development Goals	2.4	2.8	2.0	2.59	1.83	2.7	High	

Source: Targeted survey. Cells with red boundary lines indicate lack of internal consensus within the stakeholder group and the average score should be considered indicative.

Internal coherence

The targeted survey indicated that respondents found the legislation moderately coherent internally. Industry rated the internal coherence the highest out of the stakeholder groups while academics the lowest with a lack of consensus within that stakeholder group.

Within the open-ended questions, when asked about the most and least coherent aspects of the legislation or for additional comments in the public consultation, responses focussed on specialised and complementary legislations rather than internal coherence. Within the interviews, respondents were generally positive about the coherence of the legislation remarking that there were no major problems and that the components of the legislation were synergistic.

The legal analysis and literature review on internal coherence of the EU general pharmaceutical legislation has not led to the identification of issues of coherence. There are strong linkages between Directive 2001/83/EC and Regulation (EC) No 726/2004**.** They contain multiple cross-references to the other legal text and common requirements (e.g. same definitions, some prohibitions for non-authorised medicinal products) ensuring their internal coherence despite they cover two types of authorisation procedures.

Coherence with specialised pharmaceutical legislation

Main findings

Medicines for children (Paediatric Regulation)

- National rules on the conduct of trials with children lead to delays on the completion of paediatric investigation plans and risk to undermine the complementarity between these pieces of legislation
- Better coordination between committees needed
- Suggestions from stakeholders to integrate this regulation within the EU general pharma legislation to address, inter alia, issues related to data exclusivity on old active substances

Medicines for rare diseases (Orphan Regulation)

- Lack of coherence as regards generic entry
- Better coordination between committees needed

Regulation on advanced therapy medicinal products (ATMP)

- Lack of clarity on definition of ATMP and potential misclassification with borderline products
- Better coordination between committees needed

- *Medicines for children (Paediatric Regulation)*[41]

Pursuant to Article 2 of the Paediatric Regulation the definitions of Directive 2001/83/EC are applicable to the Regulation on medicines for children. Article 7 of the Regulation coordinates the legal status of medicines authorised prior to the entry into force of the Regulation. Article 9 limits the scope of application of the Regulation to certain products designated in Directive 2001/83/EC. Most importantly, Article 27 sets out the *lex specialis* nature of the Regulation and recalls the role of the general pharmaceutical legislation for authorisations of medicinal products. Article 47 sets out the principle of differentiated fees for the authorisation of paediatrics in link with Regulation 726/2004. In the Evaluation of 2020, the European Commission states that "the Paediatric Regulation mostly interacts in a coherent manner with related EU and national legislations and measures".[42] The objectives of this legislation are generally aligned with the ones set out by the general pharmaceutical legislation. However, the Evaluation adds that national rules on the conduct of trials with children may still delay the completion of a paediatric investigation plan (PIP). Achieving better compliance checks for PIPs is essential to not undermine the complementarity of this legislation. The Evaluation also underlines that despite five members of the Paediatric committee are appointed by the Committee for Medicinal Products for Human Use a better coordination between these committees may be beneficial to ensure that applicants have sufficient data for the use of their paediatric product to submit a successful market authorisation request, which is one of the aims of the Paediatric Regulation. According to the respondents of the targeted survey, the Paediatric regulation was viewed as not very efficient nor coherent with the general legislation resulting in duplication of very similar processes in the general legislation as concerns unmet need. Multiple respondents suggested it would be better integrated within the framework of the general legislation and that this would also address some issues that arise from data exclusivity on old active substances. Academic stakeholders highlighted that legislation needs to be more favourable to promote development of new paediatric indications where it currently focusses only repurposing medicines authorised for use in adults for children.

- *Medicines for rare diseases (Orphan Regulation)*[43]

According to the 2020 Evaluation (SWD/2020/0163 final) the Orphan Regulation does not interact in a coherent fashion with the Directive on Medicinal Products for Human Use (2001/83/EC) as regards generic entry. This is because, for orphan medicinal products, generic competitors can only submit an application for marketing authorisation at the end of the 10-year protection period; on the contrary, the data and market protection periods applicable to all human medicines allow generic competitors to directly place generics on the market at the end of the 10-year protection period. This difference may delay generic entry for orphan medicinal products. One of the aims of the ongoing revision of the orphan regulation is to improve availability and accessibility. This would also imply that generic entry is happening for products where the market exclusivity expired (something that the European Commission is currently checking in the ongoing Impact Assessment for the revision of the Orphan Regulation). The ongoing supporting study for the

[41] Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) 1768/19, Directive 2001/20/EC. Directive 2001/83/EC and Regulation (EC) No 726/2004, OJ L 378, 27.12.2006, p. 1

[42] COMMISSION STAFF WORKING DOCUMENT EVALUATION Joint evaluation of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products. SWD/2020/0163 final

[43] Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products, OJ L 18, 22.1.2000, p. 1.

Impact Assessment for revision of the orphan Regulation should bring more clarity about the exact reasons why this entry has been limited so far. This may relate to inconsistencies between the orphan legislative framework and the general pharmaceutical framework, but also to other factors (e.g. other regulatory (IP) protections may still exist after expiry of the market exclusivity or economic factors related to a limited patient population, also in possible other jurisdictions like the US).

The 2020 Evaluation (SWD/2020/0163 final) also underlined that the Committee for Medicinal Products for Human Use and the Committee for Orphan Medicinal Products use different timelines for their assessments and sponsors submit different data to each committee; as a result, the Committee for Orphan Medicinal Products process is not well integrated in the Committee for Medicinal Products for Human Use process, which may lead to delays in some cases. Therefore, it may be beneficial to aim for better coordination between these scientific committees, which should lead to faster assessment of marketing applications.

Finally, it should be added that orphan drug designation is strongly appealing, compared with ordinary routes for drug approval,[44] especially because smaller clinical trials are the norm, and broader disease markets can be accessed after approval.[45] If the drug is genuinely intended for an orphan use, then this is acceptable; but in other instances, it might be a disingenuous short cut around the requirements of the general pharmaceutical legislation. In the same vein, healthcare professionals consulted stressed that the increase in precision and personalised medicine has led to proliferation of orphan indications (taking advantage of orphan policies and incentives) which has limited competitions and does not spur development of the types of medicines for which the policies were intended. Multiple stakeholder groups, including respondents from Industry, raised issues about the misuse of orphan indications where the financially favourable legislation has encouraged 'indication stacking'.

- *Regulation on advanced therapy medicinal products (ATMP)[46]*

Article 3(7) of Directive 2003/81/EC explicitly excludes ATMP as defined in the ATMP from the scope of application of the Directive. Further institutional arrangements aim to ensure the coherence between the general legislation and the Regulation. For instance, the Standing Committee on Medicinal Products for Human Use, assisting the European Commission, is the same for general medicinal products and ATMP. Furthermore, the Committee for Medicinal Products for Human Use must consult the Committee for Advanced Therapies in certain cases. Nevertheless, multiple groups of stakeholders raised a lack of clarity on definition of ATMP and potential misclassification with borderline products (e.g., medical devices containing pharmaceuticals), as well as differing interpretations (and resultant classifications) and regulation in member states. This was indicated to be particularly true for new and emerging medicinal products which lack a regulatory space where definitions do not keep up with technology. The overlap or boundary with BTC was raised a becoming increasingly nebulous with concerns over mission creep that would result in hospital approved ATMPs, which may result in uneven level playing field and potentially compromises safety.

The 2020 Evaluation (SWD/2020/0163 final) also underlined that the Committee for Advanced Therapies and the Committee for Medicinal Products for Human Use use different timelines for their assessments and sponsors submit different data to each committee; as a result, scientific discussion can be difficult as the committees lack common ground, which can adversely affect the outcome or the timing.

Finally, the implementation of Article 28 of Regulation 1394/2007, referred to as the hospital exemption, is problematic in some cases and needs to be flagged. The hospital exemption permits Member States to authorise the development and manufacture of ATMPs in the absence of a marketing authorisation provided that certain conditions are met, including the preparation on a non-routine basis and that quality (including GMP) and pharmacovigilance requirements under pharma framework are complied with. The implementation of the hospital exemption has given

[44] Thomas S, Caplan A. The Orphan Drug Act Revisited. JAMA. 2019 Mar 5;321(9):833-834. doi: 10.1001/jama.2019.0290. Erratum in: JAMA. 2019 Aug 6;322(5):469. PMID: 30768155.
[45] Sarpatwari, A., & Kesselheim, A. S. (2019). Reforming the Orphan Drug Act for the 21st Century. New England Journal of Medicine, 381(2), 106–108. https://doi.org/10.1056/nejmp1902943
[46] Regulation (EC) No 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004, OJ L 324, 10.12.2007, p. 140.

rise to concerns that in some Member States unproven or substandard treatments are given to patients.

Coherence with other EU health legislation

Main findings
EMA fees Regulation • Coherence with sectorial and cross-cutting legislation • According to some public authorities and industry stakeholders, EMA fees do not adequately compensate NCAs' work under the centralised procedure **BTC legislation** • Difficulties concerning the classification of a substance/product as a BTC or as a medicinal product and the establishment of the respective applicable legal framework **Clinical trials Regulation** • One of the higher rated areas of coherence • Issues for borderline products **Medical devices Regulation** • Difficulties regarding combination product, when the medicinal substance if used separately can be considered a medicinal product. • Unclear definition and differing interpretations at national level. • The less stringent requirements of the medical devices' regulation may create safety risks for patients. **Cross-border Healthcare Directive** • Lack of clarity regarding the recognition of restricted medical prescription and the classification for the dispensing of homeopathic medicinal products • Not complete alignment regarding the definition of "prescription" **GMOs Directives** • Doubts raised by Member States regarding the application of some provisions of the general pharma legislation to medicinal products put on the market for emergency or compassionate use • Several issues caused by a lack of common approach for the assessment of GMO aspects of clinical trials with investigational medicinal products for human use **Health Technology Assessment Regulation** • The legal architecture of the HTAR is well articulated with the general pharmaceutical legislation. Potential incoherence in the review processes of EMA and HTA regulators. **Transparency Directive** • No legal incoherence. Improved enforcement by the EC on approvals by Member States and specific requirements on information given by MAH could improve access to medicines for patients. • Pre- and post-approval evaluations could further inform reimbursement/pricing decisions. **Radiopharmaceuticals under the BSSD** • Lack of specialised definitions in the general pharmaceutical legislation. • Discrepancies in the requirement for information on fixed doses (e.g., per weight) in the general authorisation procedure and the tailor-made imperatives of radiopharmaceuticals. • The complex authorisation procedure of the general pharmaceutical legislation limits the development of new treatments. **Food additives** • No legal incoherence. Synergies in the evaluation of additives in medicines and food have been identified (e.g., titanium dioxide). **Patent protection rules** • SPC: Complex overlay and suboptimal interplay of rules between regulatory exclusivity rights (data protection/market exclusivity) and intellectual property rights (patents and IPC). • SPC: Rules for compulsory licensing may require streamlining with the general pharmaceutical legislation. • UPP: The Unitary Patent Protection Regulation and general pharmaceutical legislation could bring synergies for MAHs but potential limitations have been identified.

- *EMA fees Regulation*[47]

The EMA fees Regulation sets out the fee for the various procedures of authorisation defined in the general pharmaceutical legislation as well as annual fees for maintenance activities. As such, it acts in parallel and does not appear to impact coherence. In the 2019 Evaluation of the EMA fees legislation the Commission states that "overall, the fee system is coherent with sectorial and cross-cutting legislation".[48] Nevertheless, there was a lack of consensus from public authorities on the coherence with EMA fees which when investigated geographically suggested Eastern Europe were more satisfied with coherence in this area that other European geographies. Some public authorities are of the view that the EMA fees do no longer adequately compensate NCAs for their increasing role in the centralised procedure and by consequence, high quality scientific evaluation of marketing authorisation applications is becoming increasingly challenging because the NCAs' work for centralized procedures is not cost-effective. Industry respondents also recognised this issue and were in favour that NCAs should be adequately resourced and compensated through this process. According to some academic stakeholders, financing of EMA is too reliant on private funding through pharmaceutical companies and may create some tension considering its role as a public body.

- *BTC legislation (blood,*[49] *tissues and cells*[50]*)*

The 2019 Evaluation of the Union legislation on blood, tissues and cells states that there is a direct link between the BTC directives and the medicinal product legislation.[51] Article 2(1) of both Directives draws the line of the application between the two pieces of legislation (blood or tissues and cells on the one side and Directive 2001/83/EC on the other side). However, classifying a substance/product as a BTC or as a medicinal product or establishing which of the respective legal framework applies can be difficult. According to the 2019 evaluation "while most BTC based substances/products fall clearly into either the medicinal or BTC legal framework (…) in some cases it is challenging to decide on classification and determine which legislation applies".[52] This issue has also been raised unanimously by stakeholders: the incoherence centred around unclear or unagreed definitions, differing interpretations at national level and differing regulation of different product types in different Member States.

With regard to the EU blood directive, the key interface relates to plasma that can be manufactured into plasma derived medicinal products. While the collection of this plasma falls under the blood directive, the manufacturing and following steps fall under the pharma legislation. The incoherence relates to plasma collected outside the EU and then manufactured and/or used within the EU. A lot of this plasma comes from the U.S. (about one fourth) where equivalent, but not identical, criteria apply. Overall, there is a good coordination covering inspection practices.

The tissues and cells framework applies to tissues and cells unless another legal framework applies on manufactured TC products. This framework therefore only applies on the donation, collection and testing. Thus, it is very important to understand when the EU general pharmaceutical framework applies ('industrial process' and 'intention to place on the market' – Article 2 of Directive 2001/83) and consequently when the ATMP framework applies ('substantial manipulation', 'non-homologous use' - Article 2 of regulation 1394/2007). These different definitions are not well described and leave a lot of room for interpretation.

- *Clinical trials Regulation*[53]

The main legal interconnections between this instrument and the general pharmaceutical legislation seem to create a coherent framework. The regulation was considered one of the higher

[47] Council Regulation (EC) No 297/95 of 10 February 1995 on fees payable to the European Agency for the Evaluation of Medicinal Products and Regulation 658/2014

[48] COMMISSION STAFF WORKING DOCUMENT EVALUATION of the European Medicines Agency's fee system. SWD(2019) 336 final.

[49] Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC. OJ L 33, 8.2.2003, p. 30–40.

[50] Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. OJ L 102, 7.4.2004, p. 48–58.

[51] COMMISSION STAFF WORKING DOCUMENT Evaluation of the Union legislation on blood, tissues and cells. SWD(2019) 376 final.

[52] Ibid.

[53] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC Text with EEA relevance. OJ L 158, 27.5.2014, p. 1–76.

rated areas of coherence by stakeholders. Only the industry sector pointed out inconsistencies regarding the advice received from different working groups at the EU level. More precisely, clinical trial application phase in national Member States is followed by multiple committees and scientific advisory components that are not joined up despite looking at the same product. In the "old" directive 2001/20 system, there were no mechanisms to harmonise at the European level. Regulation 536/2014 aims to harmonise the scientific elements for multinational trials, although the final decision on a clinical trial remains a Member State prerogative. This leads in some cases to incoherence between the processes for marketing authorisation (and the scientific advice given at European or Member State level) and the clinical trial authorisation process.

It should also be added that the borderline products' definition issues seen for medical devices and BTC arise also for the clinical trials, as the main definitions apply and are decisive on whether research is a clinical trial or not.

- *Medical Devices Regulation*[54]

Article 1(6) of the Medical Devices Regulation excludes medicinal products as defined in Directive 2001/83/EC from its scope and sets the 'principal mode of action of the product' as the primary criterion to distinguish between medicinal products and medical devices. Nevertheless, difficulties arise when a medical device incorporates substances which if used separately can be considered medicinal products and thus being able to receive market authorisation at national level. Stakeholders centred their critics around unclear definitions and differing interpretations at national level – which leaves stakeholders and patients in unequal position in different Member States – calling for a harmonisation of definitions and processes. EMA remains the only major pharmaceutical regulatory body that is not also in charge of medical devices. Thus, a point of contention is whether the pharmaceutical legislation is coherent with the Medical Devices Regulation when the latter has apparently less demanding regulatory standards, affecting the relative safety profiles of drugs and devices.[55] The tensions are particularly strong for drug-device combination products, and clinical pathways where a device or drug could be recommended. The disparity in regulation could distort medical markets, put pressure on patient safety and access, and generate other inefficiencies from lack of integration.

- *Cross-border healthcare Directive*[56]

The Directive has several legal interlinkages with the general EU pharma legislation. This Directive must apply without prejudice to the Medicinal Products Directive (Article 2.h) and Regulation (EC) No 726/2004 (Article 2.l); moreover, a medicinal product is defined by reference to the Medicinal Products Directive (Article 3.i). The cross-border recognition of a prescription is conditional on the authorisation in the territory of the MS of a medicinal product based on Directive 2001/83/EC or Regulation 726/2004 (except for special medical prescriptions pursuant to Article 71 of the Medicinal Products Directive). Nevertheless, this provision does not apply to medicinal products subject to special medical prescription provided for in Article 71(2) of Directive 2001/83/EC (Article 11.6 of Directive 2011/24/EU). However, Directive 2001/83/EC also foresees 'restricted' medical prescription, reserved for use in certain specialised areas. It is not clear whether and how such prescriptions should be recognised under the Cross-border Healthcare Directive.

It should be added that Directive 2001/83/EC and the Cross-border Healthcare Directive's definitions of "prescription" are not completely aligned. Directive 2001/83/EC defines "Medicinal Prescription" as any medicinal prescription issued by a professional person qualified to do so. The Cross-border Healthcare Directive defines "prescription" as prescription for a medicinal product […] issued by a member of a regulated health profession within the meaning of Article 3(1)(a) of Directive 2005/36/EC who is legally entitled to do so in the Member State in which the prescription is issued. Related to this, the CJEU interpreted the definition of "prescription" within the meaning of the Cross-border Healthcare Directive and stated that the term does not comprise order forms issued by a health professional in another Member State that do not contain the name of the patient concerned.[57]

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[54] Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC. OJ L 117, 5.5.2017, p. 1–175.

[55] Pane J, Coloma PM, Verhamme KM, Sturkenboom MC, Rebollo I. Evaluating the Safety Profile of Non-Active Implantable Medical Devices Compared with Medicines. Drug Saf. 2017 Jan;40(1):37-47.

[56] Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare. OJ L 88, 4.4.2011, p. 45–65

[57] Judgment of the Court (Fifth Chamber) of 18 September 2019. VIPA Kereskedelmi és Szolgáltató Kft. v Országos Gyógyszerészeti és Élelmezés-egészségügyi Intézet. EU:C:2019:751.

- Article 14(1) of Directive 2001/83/EC refers to the classification for the dispensing of homeopathic medicinal products. The Cross-border Healthcare Directive concerns dispensing medicinal products on a prescription issued in another Member State. It is not clear however, what kind of classification for the dispensing is meant in Article 14(1) of Directive 2001/83/EC and how it could affect the recognition of prescriptions under the Cross-border Healthcare Directive. *GMOs Directives*[58]

The Union legislation on GMOs encompasses Directive 2009/41/EC on the contained use of genetically modified microorganisms and Directive 2001/18/EC on the deliberate release into the environment of GMOs. Medicinal products that have been granted an EU or national marketing authorisation in accordance with Regulation 726/2004 and Directive 2001/83, respectively, are exempted from Directive 2001/18/EC and Directive 2009/41/EC. The evaluation of the environmental impacts of medicinal products for human use that contain or consist of GMOs is done, in accordance with the principles set out in Directive 2001/18/EC, by the European Medicines Agency or the national competent authority, as applicable, in the context of the assessment of the marketing authorisation application pursuant to the medicinal product legislation. Conversely, the administration of medicinal products that have not been granted a marketing authorisation in accordance with Union legislation is not exempted from the GMO legislation. This is the case, for example, for investigational medicinal products. There is an interlink between the scopes of the pharmaceutical legislation and of the GMO legislation, i.e. medicinal products containing or consisting of GMOs. The objectives are consistent, i.e. protection of human, animal health and the environment.

However, there are many concerns that the GMO Directive impedes the proper functioning of the general EU pharma legislation due to the complexity of national implementing legislation for the GMO requirements. More specifically, Recital 23 of Regulation (EU) 2020/1043[59] indicates that doubts have been raised by some Member States regarding the application of the provisions of Directive 2001/18/EC and Directive 2009/41/EC in the situations contemplated in Article 5(1) and (2) of Directive 2001/83/EC and Article 83 of Regulation (EC) No 726/2004. These provisions allow Member States to authorise the supply and administration of medicinal products for human use (including medicinal products that contain or consist of GMOs) in the absence of a marketing authorisation where there is an urgent need to address the specific needs of a patient, for compassionate use, or in response to the suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation that could cause harm. In other words, the Recitals in Regulation 2020/1043 explain the perceived lack of coherence between Member States' implementation of the GMO directives and general pharma legislation. Recital 10 states that it is "particularly difficult to conduct multi-centre clinical trials with investigational medicinal products that contain or consist of GMOs involving several Member States" and Recital 17 adds that the "requirement to satisfy environmental risk assessment and consent under Directives 2001/18/EC and 2009/41/EC can involve high administrative burden due to variation in Member State law". The exceptions inserted in Regulation (EU) 2020/1043 ensures that the conduct of clinical trials in the territory of several Member States with investigational medicinal products containing or consisting of GMOs intended to treat or prevent COVID-19 is not delayed, but for medicinal products other than COVID-19 preventions and treatments, the concerns are on-going; this is because the exceptions pursuant to Part B of Directive 2001/18/EC do not clearly cover medicinal products permitted by the general pharmaceutical legislation to be put on the market for emergency or compassionate use.

This issue has also been raised by stakeholders, that outlined that different national implementations on GMO assessments lead to very complex multinational clinical trials.

Regulation (EC) 536/2014 on clinical trials is without prejudice to the application of the GMO Directives. There is not a common approach for the assessment of GMO aspects of clinical trials with investigational medicinal products for human use in the EU as some Member States apply Directive 2001/18/EC, other Member States apply Directive 2009/41/EC and others decide on a case-by-case basis or apply both. In the Commission's study on new genomic techniques (NGT)[60], Member States and stakeholders noted the challenges of applying the current GMO legislation to

[58] Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC. OJ L 106, 17.4.2001, p. 1–39 and Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the contained use of genetically modified micro-organisms. OJ L 125, 21.5.2009, p. 75–97.

[59] Regulation (EU) 2020/1043 of the European Parliament and of the Council of 15 July 2020 on the conduct of clinical trials with and supply of medicinal products for human use containing or consisting of genetically modified organisms intended to treat or prevent coronavirus disease (COVID-19). OJ L 231, 17.7.2020, p. 12–16.

[60] Study on the status of new genomic techniques under Union law and in light of the Court of Justice ruling in Case C-528/16. SWD(2021) 92 final.

medicinal products for human use. In particular, for clinical trials, some Member States reported that there are doubts as to which techniques and products are subject to the GMO legislation. Stakeholders from the medicinal sector consider that the GMO legislation is not specifically designed for medicinal products. They indicated that the application of the GMO authorisation procedures to investigational medicinal products represents a problem that hinders the development of these products, delays the conduct of clinical trials in the EU and patient access to them as well as affects the EU's competitiveness in the pharmaceutical sector. Specific problems mentioned in relation to the application of the GMO legislation include the lack of harmonisation, the duplication of assessments (under both GMO and pharmaceutical frameworks) and insufficient expertise among GMO authorities on gene therapies, in view of the rising number of applications. The labelling of NGT products raises different considerations in the medicinal sector. The traceability and labelling provisions in Directive 2001/18/EC do not apply to medicinal products, which have to be labelled in accordance with the medicines legislation. Stakeholders active in the medicinal sector believe that no additional labelling rules are needed for NGTs, beyond what is already required under the medicines framework. Several stakeholders consulted in the Commission's study on NGTs ask for reconsideration of the application of the GMO legislation to medicinal products consisting of or containing GMOs. More specifically, they believe that there are no environmental and biosafety risks for non-replicating viral vectors or GM human cells, as these do not duplicate and cannot survive in the environment. They call for a more streamlined and harmonised approach that fully integrates GMO aspects into the clinical trial application process. Also, several Member States competent authorities are in favour of a more harmonised and streamlined regulatory framework.

- *HTA Regulation*[61]

The HTA Regulation (HTAR) establishes a framework to support Member State cooperation and the measures needed for clinical assessment of health technologies. HTAR was adopted on 15 December 2021 with a date of application in January 2025, therefore no practical issues of coherence can be identified yet. The objectives and scope of the HTAR are well aligned to those of the pharmaceutical legislation. The HTAR creates the necessary legal framework for HTA bodies to carry out joint clinical assessments of health technologies, including medicines receiving central marketing authorisation (Article 7(1)(a) and (b)). The provisions of HTAR do not interfere with the legal requirements regarding the authorisation process under the pharmaceutical legislation. The provisions on Joint Scientific Consultations (JSC) to be carried out in parallel with EMA (Article 17.2 of HTAR) create the necessary legal framework for the cooperation between EMA and HTA bodies, facilitating the development of convergent views on the evidence to be generated by the drug developer to satisfy both regulatory and HTA needs. HTAR ensures appropriate articulation with the EU pharmaceutical legislation by making reference to the definitions of medicinal products and marketing authorisation procedure.

- *Transparency Directive*[62]

The aim of this Directive is to ensure that Member States measures on prices and reimbursement of medicinal products are transparent. It details the procedures that Member States must follow so that their decisions and policies do not create obstacles to the EU pharmaceutical trade. No coherence issues have been identified between the two legal regimes. To enhance the synergy between the two legal regimes, it was suggested that regulatory requirements for the evidence generated in pre- and post- approval phase (in particular in case of conditional MA or adaptive pathways) under the EU general pharmaceutical legislation could also cover the needs of the subsequent processes and decision-making at national level (e.g. HTA, pricing and reimbursement). It was stressed during the consultation (industry) that the lack of enforcement by the Commission of the Member States obligation to adopt a decision on the application on price and reimbursement by MAHs impacted the general pharmaceutical legislation in terms of pricing and reimbursement of medicines. In the same vein, another stakeholder (civil society) considers that the lack of detailed requirements on information to be provided by MAHs in pricing and reimbursement applications impacts access to medicines for patients if Member States are unable to make a reimbursement and pricing decision from the information provided.

[61] Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU (Text with EEA relevance) PE/80/2021/INIT OJ L 458, 22.12.2021, p. 1–32

[62] Council Directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of national health insurance systems

- *Directive 2013/59/Euratom laying down basic safety standards for protection against the dangers arising from exposure to ionising radiation[63] (BSSD)*

Nuclear medicine is a branch of medicine that focuses on using radioactive substances for the diagnosis and treatment of diseases. Those substances are referred to as radiopharmaceuticals[64]. They are regulated under both the EU pharmaceutical and radiation protection regimes, thus coordination in implementing the different regulatory frameworks is crucial. Currently the general pharmaceutical legislation as well as the BSSD do not include a specific provision to address all the peculiarities of radiopharmaceuticals thus creating a challenging environment for the development and roll-out of radiopharmaceuticals in the EU. The following coherence issues have been identified:

- Lack of specialised definitions for radiopharmaceuticals and their associated technologies: Directive 2001/83/EC does provide several important definitions pertaining to radiopharmaceuticals; however, those are not sufficiently up to date to cover the newly emerged technologies. This refers particularly to the definitions of "radionuclide precursor radiopharmaceuticals" and "radionuclide precursor"[65].
- Inconsistencies with dosage requirements: The BSSD requires individually planned dosimetry of all radiotherapeutic procedures, however, this is not supported by the marketing authorisation requirements of the EU general pharmaceutical legislation. The latter follows traditional dosing schemes and requests prospective MAHs to provide information on fixed doses of medicines, often adjusted based on body weight, but not tailored to the specific patient case. This approach does not fit in the radiopharmaceuticals given their safety profile and safety requirements, which requires tailor-made dosimetry, to deliver the desired therapeutic effect and protect patients. For existing licensed radiopharmaceuticals, fixed-dose values are general, often obtained from phase I or II clinical trials.[66]
- Requirements for marketing authorisation: Overall, the requirement for marketing authorisation is difficult for radiopharmaceuticals and inhibits their commercialisation in the EU. It is important to recognise the market failure factor applicable to radiopharmaceuticals. Mainly, this refers to little involvement of the pharmaceutical industry in this field given that industrial production of radiopharmaceuticals is extremely limited. The low interest from commercial actors leads to overall slower progress in the number of products authorised and a higher burden on other (mostly research and academia) actors, who are not as versed in regulatory subjects as the industry stakeholders. Particularly difficult is the requirement of Directive 2001/83 to apply for a marketing authorisation for all material used in the preparation of radiopharmaceutical products. The Directive considers only one method of production of radiopharmaceuticals, the traditional kit-based preparation, and omits the new production technologies, particularly the complex preparation form (i.e., preparation from starting materials).[67] The latter is already heavily regulated by the European Pharmacopoeia which required extensive quality control before application to the patient. Complex preparation is becoming more and more common in the EU and the Directive does not sufficiently address this development, as it requires marketing authorisation for all material used via this route.

Note that within the context of the SAMIRA action plan[68], the Commission, at the time of writing launched a call for tender to carry out a study addressing these issues and to improve the

[63] Council Directive 2013/59/Euratom of 5 December 2013 laying down basic safety standards for protection against the dangers arising from exposure to ionising radiation, and repealing Directives 89/618/Euratom, 90/641/Euratom, 96/29/Euratom, 97/43/Euratom and 2003/122/Euratom

[64] Radiopharmaceuticals are different from other types of pharmaceuticals due to several reasons (e.g. they cannot be industrially produced due to their short half-life, there is very limited interest from commercial players to enter the radiopharmaceutical markets because large-scale industrial production and distribution are impossible; radiopharmaceuticals need to be prepared from radionuclides by specialised personnel in controlled safe environments; the preparation of radiopharmaceuticals involves loading a radionuclide with a vector molecule; radiopharmaceuticals need to be administered to patients shortly after their preparation and based on individually calculated dosimetry; research and development of novel radiopharmaceuticals are performed primarily by academic research institutes, as opposed to the biotech and pharmaceutical industry for other types of medicinal products.

[65] European Commission, Directorate-General for Energy, Developments in nuclear medicine: new radioisotopes in use and associated challenges: EU Scientific Seminar November 2019, Publications Office, 2020, https://data.europa.eu/doi/10.2833/522008.

[66] Statement by the European Association of Nuclear Medicine (EANM) Posology for Radiopharmaceuticals: contradictory legal requirements between BSS Directive 2013/59/Euratom and EMA marketing authorisations schemes. December 2021

[67] Statement of the European Association of Nuclear Medicine (EANM) for a better inclusion of the particularities of Radiopharmaceuticals within the Review of Directive 2001/83EC on Pharmaceutical Legislation. December 2021

[68] COMMISSION STAFF WORKING DOCUMENT on a Strategic Agenda for Medical Ionising Radiation Applications (SAMIRA) Brussels, 5.2.2021 SWD(2021) 14 final available at:
https://ec.europa.eu/energy/sites/default/files/swd_strategic_agenda_for_medical_ionising_radiation_applications_samira.pdf

understanding of the links and the interdependencies between the European pharmaceutical legislations and the Euratom radiation protection requirements[69].

- *Regulation (EC) No 1333/2008 on food additives[70]*

The list of authorised food additives, related restrictions and prohibitions of use under Regulation (EC) No 1333/2008 also applies to food additives in medicinal products[71]. Article 2 of Regulation (EC) No 1333/2008 on the scope does not include any reference to the possibility of exempting medicinal products. There are some coordinated interactions between EU regulators on food additives and on medicinal products as demonstrated in the case of titanium dioxide. On 17 May 2021, the EC requested the EMA to provide an analysis defining the technical purpose of Titanium dioxide in medicinal products; feasibility of alternatives without negative impact on the quality, safety and efficacy of medicines; and if confirmed, considerations to be taken into account to define a transition period for phasing out this excipient. The EC has adopted a Regulation[72] withdrawing the authorisation to use titanium dioxide (TiO2 also known as E171) in food products. This withdrawal however does not apply to uses in medicinal products. Article 3 of this Regulation requires the Commission, following a consultation of the EMA, to review the necessity to maintain or delete titanium dioxide from the Union list of food additives for the exclusive use as a colorant in medicinal products in Part B of Annex II to Regulation (EC) No 1333/2008 within three years after the date of entry into force of this Regulation.

- *Supplementary protection certificate[73] and unitary patent certificate[74]*

Regulation (EC) No 469/2009 establishes a supplementary protection certificate for producers of pharmaceutical products and plant protection products to offset the loss of patent protections due to the compulsory lengthy testing and clinical trials. The IA conducted for Regulation (EU) 2019/933 amending Regulation (EC) No 469/2009 concerning the supplementary protection certificate for medicinal products, as well as its recitals, highlight that the SPC legislation applies without prejudice to the authorisation procedure laid down in Directive 2001/83/EC, in particular the regulation of generics and biosimilars, as well as falsified medicines, medical devices' unique identifiers, but also the GMPs.

Consultations however highlight the complex overlay and suboptimal interplay of rules between regulatory exclusivity rights (data protection/market exclusivity) and intellectual property rights (patents and IPC). Specific issues identified by stakeholders from the general public include the limitation of PIP incentives to those products which SPC as the last protection to expire, fragmentation of SPC regulation across Member States, as well as possible evergreening/overcompensation practices, leading to delay in the entry of biosimilars and generics and thus reduction of the affordability of treatments.

Besides, compulsory licensing of pharmaceutical products may be limited by IP/data protection rules, which may prevent the issuance of marketing authorisations[75]. In the same vein, academic stakeholders highlighted the strong focus of the pharmaceutical legislation on the protection of IP rights. Stakeholders from public authorities highlighted the lack of access by MAHs to manufacturers' data to control processes, and a lack of information about patent/SPC's expiration date.

Unitary patent protection

Regulation (EU) 1257/2012 sets out a unitary patent, according to which inventors may submit a single application for intellectual property protection in 25 Member States, without requiring

[69]See tendering documents at: https://etendering.ted.europa.eu/cft/cft-documents.html?cftId=9465

[70] Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives (Text with EEA relevance) *OJ L 354, 31.12.2008, p. 16–33*

[71] Regulation (EU) No 231/2012 of 9 March 2012 as amended lays down specifications on colours and sweeteners listed in Annex II (Union list of food additives approved for use in foods and conditions of use) and Annex III (Union list of food additives including carriers approved for use in food additives, food enzymes, food flavourings, nutrients and their conditions of use) to Regulation (EC) No 1333/2008 also applies to medicinal products.

[72]Commission Regulation (EU) 2022/63 of 14 January 2022 amending Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council as regards the food additive titanium dioxide

[73] Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the supplementary protection certificate for medicinal products.

[74] Regulation (EU) No 1257/2012 of the European Parliament and of the Council of 17 December 2012 implementing enhanced cooperation in the area of the creation of unitary patent protection.

[75]Hoen, Ellen & Boulet, Pascale & Baker, Brook. (2017). Data exclusivity exceptions and compulsory licensing to promote generic medicines in the European Union: A proposal for greater coherence in European pharmaceutical legislation. Journal of Pharmaceutical Policy and Practice. 10. 10.1186/s40545-017-0107-9, available at https://www.researchgate.net/publication/318120659_Data_exclusivity_exceptions_and_compulsory_licensing_to_promote_generic_medicines_in_the_European_Union_A_proposal_for_greater_coherence_in_European_pharmaceutical_legislation, viewed 13 January 2022.

validation in all Member States and with equal protection. It is expected to apply from the second half of 2022. The unitary patent protection could bring synergies with the centralised authorisation procedure of pharmaceutical products by the EMA, boosting regulatory attractiveness.

However, possible limitations include the proportionate character of the duration and scope of market exclusivity granted to pharmaceuticals in view of the risk and investment in innovation and authorisation procedures. Moreover, recital 10 of Regulation (EU) 1257/2012 upholds the concept of compulsory licensing by each Member State within their territory, which requires alignment with pharmaceutical legislation, data protection and market exclusivity.

Coherence with non-health related EU legislation

Main findings
GDPR and EUDPR • Lack of clarity regarding the interpretation and application of GDPR in healthcare and pharmaceuticals • Confusion linked to the definition of consent
Regulation on drug precursors • More coordination could be beneficial, in particular to tackle the production of illegal substances via finished medicinal products, e.g., (pseudo)ephedrine.
Chemicals legislation (REACH) • Coordination is generally achieved. Some gaps have been identified in relation to environmental risk assessment obligations compared to • REACH would limit the production of APIs.
EU Water legislation • Policy actions to mitigate the impact of medicinal products in water will be in place with the revision of the Environmental Quality Standard Directive (2008/108/EC as amended by 2013/39/EU), revision of the Groundwater Directive (2006/118/EC) and the revision of Waste Water Treatment Directive (91/271/EEC). However, this will imply additional compliance costs for the Member States. • Only a limited set of pharmaceuticals can be targeted effectively with this legislation (i.e. those monitored in most parts of the EU and posing the biggest risk to nature / human health), leaving the majority of pharmaceuticals unaddressed. • Currently, updates to guidance are necessary for effective monitoring of pharmaceuticals in water and information/coordination between authorities appears insufficient.
Competition law • Concentration at industry level, with specific concerns on the innovativeness of the European pharmaceutical industry. • Insufficient resources to conduct competition inspections in the pharmaceutical industry.
Chemicals Strategy for Sustainability • No reference to the Strategy actions under the general EU pharmaceutical legislation.
Action plan on antimicrobial resistance • The general pharmaceutical legislation lacks provisions to regulate the use of antimicrobials and to incentivise the authorisation of new antimicrobials.

- *General Data Protection Regulation (GDPR)[76] and EU Data protection Regulation (EUDPR)[77]*

The GDPR and the EUDPR provide a horizontal framework for the processing of personal data, ensuring that it happens "for a good reason, transparently, and securely". Article 9 of the GDPR and 10 EUDPR set out lawful grounds for the processing of special categories of data (including

[76] Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation). OJ L 119, 4.5.2016, p. 1–88.

[77] Regulation (EU) 2018/1725 of the European Parliament and of the Council of 23 October 2018 on the protection of natural persons with regard to the processing of personal data by the Union institutions, bodies, offices and agencies and on the free movement of such data, and repealing Regulation (EC) No 45/2001 and Decision No 1247/2002/EC. OJ L 295, 21.11.2018, p. 39–98.

heath data) such as scientific research (j) and reasons of public interest in the area of public health (i). The two data laws and the general pharmaceutical legislation complement each other because the GDPR and the EUDPR set out frameworks for processing personal data with well-considered checks and balances; thus, given that they apply horizontally, also the processing of personal data in the context of activities regulated by pharmaceutical legislation needs to comply with it. However, some coherence issues exist. These laws, in some ways, make it difficult to achieve the objectives of the general pharmaceutical legislation. Regarding the GDPR, it is unclear whether and when universities and private companies can rely on Art. 9(j) as a lawful ground for processing data and this makes the provisions in the GDPR for research "complex, dispersed and layered".[78] Moreover, there is a high level of variability from clinical trial ethics committees, data protection advisers and organisations about requirements for anonymisation, for consent for future research uses, and for allowing data subjects to withdraw (while meeting obligations to retain data to verify results);[79] stakeholders' view confirmed that the interpretation and application of GDPR in healthcare and pharmaceuticals is not clear and that guidelines would potentially help to address this issue. Aiming to more clarity by solving these problems would be beneficial giving that gathering data for authorisation of medicinal products is increasingly international and data intensive.

Finally, taking into consideration both data protection laws, there is sometimes confusion between "consent" as a legal basis/condition for processing data in the sense of GDPR and EUDPR and "informed consent" in the sense of informed consent to participate in a clinical trial or more generally, to a medical intervention. The fact that a medical treatment happens with "informed consent" does not mean that the processing of personal data that happens as part of providing the treatment (documentation of intervention in health records, billing for treatment) necessarily use "consent" under GDPR and EUDPR as the lawful basis for processing. The European Data Protection Board has provided guidance clarifying this issue in the context of clinical trials.[80]

- *Regulations on trade in drug precursors*[81]

Drug precursors are chemicals that are primarily used for the legitimate (legal) production of a wide range of products including medicinal products. However, they can also be misused for the illicit (illegal) production of drugs such as amphetamines, heroin or cocaine. For about 5-10 years, illegal drug producers in the EU have increasingly used 'designer-precursors'. Designer-precursors are close chemical relatives of traditional drug precursors, and their purpose is to circumvent the controls. They usually do not have any known legitimate use. Two EU regulations set measures to control these illicit uses. Regulation (EC) No 273/2004 establishes harmonised measures for the intra-Union control and monitoring of certain substances frequently used for the illicit manufacture of narcotic drugs or psychotropic substances with a view to preventing the diversion of such substances. Regulation (EC) No 111/2005 lays down rules for the monitoring of trade between the Community and third countries in certain substances frequently used for the illicit manufacture of narcotic drugs and psychotropic substances. More coordination between the EU general pharmaceutical legislation and these two regulations could be envisaged in particular to tackle the following concerns:

- Ephedrine and pseudoephedrine (to make methamphetamines) are extracted from medicines legally purchased over the counter in pharmacies. In such case these precursors are not 'diverted' in the sense of Regulation (EC) 273/2004 and therefore the diversion monitoring and control under this Regulation is not applied to such situation. These medicines are highly regulated in some Member States, in pharmacies (because they are often misused in certain Member States for making methamphetamine in small-scale kitchen labs). For instance, they can only be sold in very small doses for personal use. However, in pharmacies in neighbouring countries the monitoring may be much less strict. This triggers individuals to shop around in the pharmacies of these neighbouring countries and reintroduce the (pseudo)ephedrine in specific Member States for illegal methamphetamines production.

[78] Dept for Digital, Culture, Media and Sport, *Data a New Direction* (2021) , available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1022315/Data_Reform_Consultation_Document__Accessible_.pdf

[79] NIH, *Implications of GDPR for US-EU Cooperation in Biomedical Science: Observations from the US National Institutes of Health* (2019). Available at: http://www.iscintelligence.com/archivos_subidos/robert_eiss_gdpr_us-eu_cooperation_in_biomedical_science_isc_gdpr_seminar_19_nov_2019.pdf

[80] EDPB, Opinion 3/2019 concerning the Questions and Answers on the interplay between the Clinical Trials Regulation (CTR) and the General Data Protection regulation (GDPR)

[81] Regulation (EC) No 273/2004 of the European Parliament and of the Council of 11 February 2004 on drug precursors and Council Regulation (EC) No 111/2005 of 22 December 2004 laying down rules for the monitoring of trade between the Community and third countries in drug precursors.

- For the export of medicinal products containing (pseudo)ephedrine or its salts, an export authorisation is required under Regulation (EC) 111/2005 but no general licence or registration as for the other drug precursors which may lead to some difficulties for competent authorities in charge of implementing and enforcing the export authorisation requirement since they would not be aware of the economic operators involved in this activity.

- *REACH*[82]

REACH is the cornerstone of the EU legislation on chemicals. Companies must register substances they intend to place on the market. ECHA evaluates the compliance with the registration dossiers, the EU Member States are entitled to evaluate substances registered based on concern for human health or for the environment. Scientific committees assess whether risks linked to substances placed on the market can be managed. As a result, the use of hazardous substances if their risks are unmanageable can be banned or subject to restrictions or a prior authorisation[83].

According to Article 2(5) of REACH, to the extent that a substance is used in medicinal products for human or veterinary use, REACH Title II on Registration, Title V on Downstream users, Title VI on Evaluation, and Title VII on authorisation do not apply. According to Article 2(6) of REACH, medicinal products for human or veterinary use, in the finished state and intended for the final user, are exempted from information requirements through the supply chain (Title IV of REACH). Moreover, the exemption from REACH registration requirements for substances manufactured or imported for PPORD purposes can be extended for an additional five years in the case of substances intended for use in medicinal products. Certain substances used in medicinal products within the scope of the EU general pharmaceutical legislation are also exempted from certain restrictions under Annex XVII of REACH[84]. Some deadline extensions also exist for substances that are subject to the REACH authorisation procedure when they are used in medicinal products[85].

According to the REACH evaluation report[86], an information gap exists in relation to the environmental risks related to the manufacturing or formulation stages of medicinal products for human and veterinary use as a result of their exemption from REACH. Consulted public authorities consider that REACH impedes the provision of some synthesis on APIs. According to a representative of the civil society consulted, the EU general pharmaceutical legislation should give the EMA a mandate to promote alternative methods and ensure animal testing as a last resort in line with REACH requirements.

- *EU Water legislation (i.e., Water Framework Directive[87] and EQS Directive[88])*

The Water Framework Directive sets specific measures for the progressive reduction of discharges, emissions, and losses of priority substances[89] and the cessation or phasing-out of discharges, emissions, and losses of priority hazardous substances[90] into water bodies. The EQS Directive establishes limits on concentrations in surface waters for priority substances listed in its Annex II. This Directive also requires the Commission to establish a watch list of substances for which Union-wide monitoring data are to be gathered for the purpose of supporting the update of the list of priority substances. It specifies that the following medicinal products Diclofenac, 17-beta-estradiol (E2) and 17-alpha-ethinylestradiol (EE2) must be included in the first watch list, to

[82] Regulation (EC) No 1907/2006 of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency

[83] Information retrieved from ECHA webpage 'Understanding REACH' available at: https://echa.europa.eu/regulations/reach/understanding-reach

[84] Substances which are classified as carcinogen category 1A or 1B in Part 3 of Annex VI to Regulation (EC) No 1272/2008, substances which are classified as germ cell mutagen category 1A or 1B in Part 3 of Annex VI to Regulation (EC) No 1272/2008, substances which are classified as reproductive toxicant category 1A or 1B in Part 3 of Annex VI to Regulation (EC) No 1272/2008 (Entry 28 Annex XVII), Chloroform (Entry 32 Annex XVII), 1,1,2-Trichloroethane (Entry 34 Annex XVII), 1,1,2,2-Tetrachloroethane (Entry 35 Annex XVII), 1,1,1,2-Tetrachloroethane (Entry 36 Annex XVII), Pentachloroethane (Entry 37 Annex XVII), 1,1-Dichloroethene (Entry 38 Annex XVII).

[85] Bis(2-ethylhexyl) phthalate, Benzyl butyl phthalate, Dibutyl phthalate, 4-(1,1,3,3-Tetramethylbutyl) phenol, ethoxylated.

[86] COMMISSION STAFF WORKING DOCUMENT Accompanying the document COMMUNICATION FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT, THE COUNCIL AND THE EUROPEAN ECONOMIC AND SOCIAL COMMITTEE Commission General Report on the operation of REACH and review of certain elements Conclusions and Actions SWD/2018/058 final

[87] Directive 2000/60/EC of the European Parliament and of the Council of 23 October 2000 establishing a framework for Community action in the field of water policy *OJ L 327, 22.12.2000, p. 1–7*

[88] Directive 2008/105/EC of the European Parliament and of the Council of 16 December 2008 on environmental quality standards in the field of water policy

[89] Priority substances are substances the present a significant risk to or via the aquatic environment, identified on the basis of risk assessment

[90] Within priority substances, priority hazardous substances are substances that are toxic, persistent and liable to bio-accumulate or which give rise to an equivalent level of concern. Annex X of the Water Framework Directive lists the priority substances.

gather monitoring data for the purpose of facilitating the determination of appropriate measures to address the risk posed by those substances. To select substances to be included in the watch list, the Commission must consider all available information including *inter alia* information gathered according to Directive 2001/83/EC.

According to Article 8(c) of the EQS Directive the Commission must develop a strategic approach to pollution of water by pharmaceutical substances. That strategic approach must, where appropriate, include proposals enabling, to the extent necessary, the environmental impacts of medicines to be taken into account more effectively in the procedure for placing medicinal products on the market._In the framework of that strategic approach, the Commission must, where appropriate propose measures to be taken at Union and/or Member State level, as appropriate, to address the possible environmental impacts of pharmaceutical substances and in particular Diclofenac, 17-beta-estradiol and 17-alpha-ethinylestradiol), with a view to reducing discharges, emissions and losses of such substances into the aquatic environment, taking into account public health needs and the cost-effectiveness of the measures proposed.

The European Union Strategic Approach to Pharmaceuticals in the Environment was adopted in March 2019[91]. It contains several actions concerning the general pharmaceutical legislation and its actors. Under Point 5.3 the Commission must in collaboration with the EMA and Member States seek to improve the level of environmental expertise in the Committees and networks involved in the environmental risk assessment of medicinal products; examine how to improve public access to the main environmental risk assessment results and relevant toxicological thresholds for medicinal products while respecting data-protection rules, emphasise to applicants the importance of submitting a completed assessment by the time of the authorisation for marketing human medicinal products, so that adequate risk management measures can be established and published. Under Point 5.4 the Commission must in collaboration with Member States and the EMA explore the possibility of reducing waste by optimising the package size of pharmaceuticals so that medicines can be dispensed in quantities better matching needs, and by safely extending use-by (expiry) dates so that fewer medicines that are still usable have to be thrown away; facilitate the exchange of best practices among healthcare professionals on the environmentally safe disposal of medicinal products and clinical waste, and the collection of pharmaceutical residues as appropriate.

Based on Article 8 of Directive 2001/83/EC on environmental risk assessment, EMA has developed guidelines on the environmental risk assessments of medicinal products for human use published in 2006[2]. These guidelines are being revised and drafts have been published in 2018 but no final version has been adopted yet[3]. Several aspects mentioned above under Points 5.3. and 5.4 of the European Union Strategic Approach to Pharmaceuticals in the Environment are covered in these draft guidelines that details the aspects to be covered by an environmental risk assessment[92] explains how a PBT[93] assessment must be carried out, sets a list of precautionary and safety measures in case environmental risks cannot be excluded[94] and a proposed labelling aimed at minimising discharge of unused medicine into the environment.

Despite the interlinkages described above, the pharmaceutical authorisation process/authorities are not formally informed when a risk for the environment is identified (e.g., when pharmaceuticals are placed on the priority substances list and or from LUCAS survey[95] monitoring presence of pharmaceuticals in soils). Similarly, when an environmental risk is identified within the authorisation process of a medicinal product this is not communicated to competent authorities that deal with environmental matters. As underlined by the evaluation report of the

[91]COMMUNICATION FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT, THE COUNCIL AND THE EUROPEAN ECONOMIC AND SOCIAL COMMITTEE European Union Strategic Approach to Pharmaceuticals in the Environment Brussels, 11.3.2019 COM(2019) 128 final

[92] Determination of physico-chemical properties, fate and ecotoxicity, trigger values for soil, groundwater and secondary poisoning, surface water, sediment, sewage treatment plant, groundwater, soil, secondary poisoning, antibiotics, endocrine active substances

[93] Persistent, bioaccumulative and toxic

[94] Such as appropriate product storage and disposal, appropriate measure regarding the use of medicinal products, appropriate disposal of unused pharmaceuticals

[95]More information on Lucas's survey: https://esdac.jrc.ec.europa.eu/projects/lucas

EU water legislation[96], there is no reference to the Water Framework Directive objectives in the legislation on human medicinal products[97].

- *EU Competition law*

In principle, there is good coherence between the EU competition legislation with its primary objective of protecting consumer welfare and the EU pharmaceutical legislation which seeks to safeguard public health. For example, Articles 101 and 102 TFEU facilitate competition based on price (allocative efficiency). They prohibit originators from abusing dominant positions (acquired largely from exclusivity rights) to impede the subsequent entry of competitors (e.g. generic / biosimilar companies). Merger controls (and to a lesser extent Articles 101 and 102 TFEU) also provide scope for protecting competition based on innovation (dynamic efficiency). Wider issues are also now being investigated by competition authorities following on from the Commission having identified certain "patent filing" and "disparagement" practices as potentially problematic in its sector inquiry report of 2009[98] and its report on competition law enforcement in the pharmaceutical sector of 2019[99]. These include potentially abusive patent management strategies, and campaigns to disparage other products.

However, room for improvement remains. There are concerns that Euro-American merger control has been too permissive due to a focus on market concentration (a measure of competition around a product) without due regard to industry concentration (a measure of competition within the industry).

Coherence with other EU and international policies

- *Chemicals Strategy for Sustainability Towards a Toxic-Free Environment[100]*

The chemical strategy was published in 2020 as part of the EU's zero pollution ambition a key commitment of the European Green Deal. It contains several actions to be implemented by the Commission. Some of these actions will have an impact on how medicinal products will be authorised produced and used to ensure a toxic-free environment such as to promote the development of safe and sustainable-by-design chemical substances, to implement the principle one substance one assessment with strong coordination between EU regulators (e.g., ECHA, EFSA, EMA) to address the impact on the environment of the production and use of pharmaceuticals in the upcoming pharmaceuticals strategy for Europe and following up the 2019 Strategic Approach to Pharmaceuticals in the Environment. Such objectives and action are not yet reflected in the EU general pharmaceutical legislation that only contains an obligation to carry out an environmental risk assessment and related EMA guidelines adopted in 2006 and currently being revised with a draft published in 2018.

- *EU Action Plan on Antimicrobial Resistance[101]*

The general pharmaceutical legislation is not coherent with the EU Strategy on Antimicrobial Resistance. It currently lacks provisions to launch access to new antimicrobials in most/all European countries; to restrict and optimise the use of antimicrobials; to achieve better labelling of antimicrobial product labels; and to promote the authorisation of new *classes* of antimicrobials (as distinct from new types falling within known classes for which resistance will develop relatively quickly).

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[96] COMMISSION STAFF WORKING DOCUMENT FITNESS CHECK of the Water Framework Directive, Groundwater Directive, Environmental Quality Standards Directive and Floods Directive 2000/60/EC of the European Parliament and of the Council establishing a framework for the Community action in the field of water policy Directive 2006/118/EC of the European Parliament and of the Council on the protection of groundwater against pollution and deterioration Directive 2008/105/EC of the European Parliament and of the Council on environmental quality standards in the field of water policy, amending and subsequently repealing Council Directives 82/176/EEC, 83/513/EEC, 84/156/EEC, 84/491/EEC, 86/280/EEC and amending Directive 2000/60/EC of the European Parliament and of the Council Directive 2007/60/EC on the assessment and management of flood risks {SEC(2019) 438 final} - {SWD(2019) 440 final}

[97] https://ec.europa.eu/info/sites/default/files/swd_2019_0439_en.pdf

[98] Final Report, Pharmaceutical sector inquiry, European Commission, Competition DG available at: https://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/staff_working_paper_part1.pdf

[99] REPORT FROM THE COMMISSION TO THE COUNCIL AND THE EUROPEAN PARLIAMENT COMPETITION ENFORCEMENT IN THE PHARMACEUTICAL SECTOR (2009-2017) European competition authorities working together for affordable and innovative medicines, Brussels, 28.1.2019 COM(2019) 17 final available at: https://ec.europa.eu/competition/sectors/pharmaceuticals/report2019/report_en.pdf

[100] COMMUNICATION FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT, THE COUNCIL, THE EUROPEAN ECONOMIC AND SOCIAL COMMITTEE AND THE COMMITTEE OF THE REGIONS Chemicals Strategy for Sustainability Towards a Toxic-Free Environment, Brussels, 14.10.2020 COM (2020) 667 final

[101] Available at: https://ec.europa.eu/health/system/files/2020-01/amr_2017_action-plan_0.pdf

7.5 Annex V. Comparative legal analysis

Summary

1. Fostering Innovation

Country	Description
AUSTRALIA	Priority review pathway for medicines for serious or life-threatening conditions. Provisional approval pathway: medicines that provide promising treatment for serious or life-threatening conditions, while clinical trials are still ongoing.
CANADA	Advanced Therapeutic Pathway: tailored assessment for ATPs without technology-specific requirements and exempting the applicants from certain requirements of the regular procedure. Priority review pathway: for medicines treating serious, life-threatening, or severely debilitating disease or condition.
CHINA	Applicants of novel chemical products, biological products: granted with the protection of their product of interest, which should be developed based on self-generated preclinical and clinical data (except safety data, data disclosed before registration application) on Chinese patient. Annual price negotiation mechanism for novel products to be listed by the basic health insurance program immediately after gaining market entry.
ISRAEL	Psifas Initiative for Precision Medicine: designed to collect health data and biological samples from hundreds of thousands of volunteers establishing a community of participants. The information obtained will accelerate the development of medical care specifically tailored to the Israeli population.
JAPAN	A premium for the development of innovative medicine has been implemented in the price calculation. Targeted total examination period: n/a New medicinal product: 12 months. Orphan medicinal products and specific use medicinal product: 9 months. Pioneering medicinal product: 6 months.
SOUTH KOREA	Research and development fund for innovative drugs: the Ministry of Health and Welfare is entitled to designate companies as innovative companies if they fulfil certain conditions (R&D investment in particular). This status gives priority to R&D projects, tax deductions and preferential treatment in drug prices. Support developers of cutting-edge biotechnologies: regulatory guidelines ensure the quality, safety and efficacy for advanced therapy medicinal products including cell therapy products, stem cell therapy products and gene therapy products.
USA	Various accelerated procedures for serious conditions lacking satisfactory treatments providing significant improvements compared to existing treatments. FDA provides personalised assistance to MAHs in developing drugs for unprofitable or unpatentable drugs for less than 200 000 patients. Application fees can be waived to protect public health, for example for small businesses. It is waived for drugs for a rare disease or condition. Wide margin of appreciation regarding the pricing decisions of MAHs, on the basis of market conditions. This is sometimes defended as a way to enhance innovation. Financial grants are granted for innovation under the Orphan Products Grant Program or via post-approval support for drugs treating a rare disease or condition.

	Market exclusivity rules vary depending on product classification, indication to be treated or the intended patient population or the level of innovation provided by a new drug. Transferrable Priority Review Vouchers can be received or purchased, granting a six-month expedite review procedure to the applicant. They are transferrable unlimitedly.

2. Accessibility and affordability of medicines

Country	Description
AUSTRALIA	A large proportion of registered prescription medicines are supplied under the Pharmaceutical Benefits Scheme (PBS) . Necessary drugs selected by an expert panel are supplied to consumers at a reduced cost due to a subsidy by the Commonwealth (federal) Government.
CANADA	The upcoming Regulations Amending the Patented Medicines Regulations will provide new factors for assessing excessive pricing (price regulatory factors of pharmacoeconomic value, market size and the gross domestic product (GDP) and GDP per capita in Canada). Canada intends to renew its Special Access Programme, which allows healthcare professionals to request medicinal products not authorised in Canada, for treating a patient with a serious or life-threatening condition where conventional treatments have failed, are unsuitable or are not available in Canada.
CHINA	Expensive new products have to go through the price negotiation process before being listed.
ISRAEL	The maximum price of a drug is set based on price in a number of European countries. It is possible that in Israel there will be a significant decrease in the price of a drug close to the date of its patent expiration in European countries, and not necessarily close to the expiration of the patent in Israel. Pharmacists have the authority to provide a generic drug even if it is registered under its trade name unless the doctor has expressly stated otherwise.
JAPAN	For generics, application can be submitted in a simplified form, using the original data from the original application and showing only bioequivalence. Detailed fees are specified according to the type and nature of the medicinal product and the content of the application. Pharmaceutical authorisation and insurance reimbursement are simultaneous. Once authorisation is obtained, the product is almost always reimbursed with a significant advantage for patients
SOUTH KOREA	System of exclusivity for the manufacturer of the first generic drug which successfully challenges the patent covering an original drug and proves bioequivalence. This exclusivity prevents the other generic drug manufacturers to market products for nine months. Bundled approval system for generic drugs: generic products from different companies produced in the same manufacturing site can be approved within the same application. Single healthcare insurance system for the reimbursement of medicinal products, covering almost all the population.
USA	Generic drugs are evaluated under the Abbreviated New Drug Application procedure, and do not require animal or human testing. A Centre for Research on Complex Generics has been established to enhance research collaboration and ensure faster marketing of complex generic drugs. Research exemption (Bolar exemption) allowing pre-authorisation research by competitors during the market exclusivity period of a medicinal product.

3. Regulatory Agility

Country	Description
AUSTRALIA	Australia applies the CHMP and EMEA guidelines for fixed combinations of medicinal products. The Generic Medicines Work-Sharing Initiative promotes the coordinated assessment of generic application files with multiple national agencies that are part of the Access Consortium (Australia, Canada, Singapore, Switzerland, United-Kingdom) Clock-stop mechanism: until a full response to the authority's request for information is submitted.
CANADA	The Ministry of Health has powers to impose terms and conditions and require a risk management plan from MAHs. Pause-the-clock mechanism: for up to 30 business days is provided in Canada.
CHINA	Conditional approval: • Life-saving medicines + critical public health needs + no alternative • Vaccines for the critical outbreak of public health events and other vaccines that are accounted for urgent needs. Rapid evaluation: • New chemical product or new traditional medicines applying for extended indication and changing formulation of the protected traditional medicines; • first application associated with an intractable and critical illness to meet the unmet clinical needs, for critical communicable diseases; • a new product for children and paediatric formulation; • urgently needed vaccines, breakthrough product, and product which meet the criteria for conditional approval. Stop the clock: to provide additional information.
JAPAN	A regulatory sandbox scheme was established in June 2018. When authorising a complex product, an application must be submitted and then the MHLW/PMDA will decide which category the product belongs to, the duration is granted according to the decided category, and there are no measures to extend or grant duration on the basis of a complex product.
USA	Personalised medicines using medicinal products and medical devices are assessed via reinforced cooperation between the respective centres responsible for drugs and medical devices within the FDA. The FDA proposed to regulate the use of artificial intelligence in medical devices' software. 3. A simple rule for combination products: they are reviewed on the basis of their primary mode of action. A "Knowledge-aided assessment and Structured Application" has been implemented using algorithms for risk assessments and computer-assisted analysis of drug applications. The FDA also ensures up-to-date knowledge of its inspectors on new technologies through trainings. Emerging Technology Program: enables the resolution of technical and regulatory issues in the assessment of new manufacturing methods.

4. Safety of supply

Country	Description
AUSTRALIA	Notification of market discontinuation and shortages to the national competent authority is required for registered Prescription Medicine, registered Controlled Drug medicines and OTC medicines included in the Therapeutic Goods Reportable Medicines Determination.

CANADA	In 2021, the Regulations Amending Certain Regulations Concerning Drugs and Medical Devices (Shortages) was adopted to prevent and mitigate shortages of key health products (medicines and medical devices).
CHINA	Comprehensive reforms of streamlining new medicines evaluation and creating efficient process of registration in 2015, have been targeting efficiency improvement and responsive review and regulatory process by resolving the backlog of new medicines evaluation and accelerating the time-to-market of novel medicines.
JAPAN	The marketing authorities are required to inform the MHLW as soon as possible (around two months) if they anticipate a supply shortage and to take appropriate measures, such as cooperation with the industry and relevant suppliers. When an authorised medicinal product is listed, the company is obliged to start manufacturing and sale of the product within three months of the date of listing, and continuously supply to medical institutions.
USA	Strategic National Stockpile of medicines and medical devices to be used in case of public health emergency. Notification of temporary or permanent marketing interruptions must occur at least six months in advance in case of a drug that is life-supporting, life-sustaining or intended for use in the prevention or treatment of a debilitating disease or condition.

4. Quality and safety of medicinal products

Country	Description
CANADA	Since 2019, the entire clinical study reports submitted by applicants and negative decisions about applications for new drug approvals are published and publicly available.
JAPAN	Re-examination system: after a certain period since the approval of a new medicinal product, manufacturers collect data from actual use in medical institutions to reconfirm the approved efficacy and safety. Good Distribution Practice (GDP) guidelines have been issued to prevent counterfeit medicines. All medicinal products are required to have a barcode to enable traceability in distribution to the medical institutions.
USA	The FDA adopted Quality Management Maturity Programs aiming at conducting onsite assessment of facility's quality management system. The final aim of the program is to incentivise investments in quality management through the development of a reward system of mature quality management systems of facilities.

6. Environmental assessment

Country	Description
CHINA	Production application of medicines must provide an Environmental Assessment Report issued by the qualified environmental assessment institutions based on the environmental monitoring data generated by the local environmental protection authorities. Environmental risk assessment is not integrated with the risk-benefit appraisal.
USA	Every application for a drug shall contain an environmental assessment and mitigation plan, to be assessed by the FDA.

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Study in support of the evaluation and impact assessment of the EU general pharmaceuticals legislation

Analytical Report

Written by Technopolis Group
For the Directorate General for Health and Food Safety
June 2022

technopolis group

DG SANTE

EUROPEAN COMMISSION

Directorate General for Health and Food Safety
Directorate D – Medical Products and Innovation
Unit D.1 – Medicines: policy, authorisation and monitoring

E-mail: sante-pharma-policy@ec.sante.eu

European Commission
B-1049 Brussel

PROJECT TEAM

Peter Varnai, Anoushka Davé, Paul Simmonds, Marisa Amato, Rebecca Babb, Ruth Dixon, Thyra de Jongh, Tatiana Paredes, Maialen Perez, Liana Petrosova, Bruno Raabe, Anneloes de Ruiter (Technopolis Group); Florent Pelsy, Maxime Moulac (Milieu Law & Policy Consulting); Aukje Mantel-Teeuwisse, Lourens Bloem, Wouter Boon, Marieke De Bruin, Jarno Hoekman, Kevin Klein, Pieter Stolk, Rick Vreman (Utrecht University); Timothy Pang, Ben Folwell (Citeline Custom Intelligence); Florian Szücs (Vienna University of Economics and Business); and Wim Spit (Ecorys BV).

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INTRODUCTION

The Analytical report focuses on reporting on secondary quantitative data analysis that was carried out as part of the the study in support of the Evaluation and Impact Assessment of the EU general pharmaceuticals legislation. It relies on existing proprietary and public databases and was used to populate pre-defined high-level indicators to assess relevant aspects of the 2004 revision of the general pharmaceutical legislation.

The empirical analyses revolve around various macroeconomic, environmental, social and technological indicators that may have been affected by the legislation. These quantitative indicators have been grouped in seven categories to address the policy elements in scope for the study with specific indicators selected to inform the main evaluation criteria of effectiveness, efficiency, coherence, relevance and EU added value of the legislation.

These indicators provide trend analysis and comparison of pre- and post-legislative periods with respect to the implementation of the 2004 revision of the general pharmaceutical legislation. Reference data from other jurisdictions was also used to assess the impact of the EU legislation.

DATA ANALYSIS

We explore the evolution of various macro-level indicators relevant for the evaluation and impact assessment of the legislation and for the new objectives identified in the 2020 pharmaceutical strategy. Considering that the revision of the legislation was announced in 2004 and implemented in the following year, wherever data allows, we present longitudinal data covering the period 2000-2020, such that one can see the evolution of a given metric across a long enough period of time that includes a pre-event period of 5 years.

The final list of specific and measurable (SMART) indicators covers:

- 13 Industrial & Economic Competitiveness (IEC) indicators
- 9 Research & Innovation (RDI) indicators
- 10 Access indicators
- 6 Affordability and Single Market (ASM) indicators
- 3 indicators related to Efficiency
- 3 indicators specific to AMR (Antimicrobial Resistance)
- 7 indicators measuring the environmental impacts

For these indicators, when data allows, we compare the pre and post legislation periods using parametric (Welch's t-test) or non-parametric (Mann Whitney U test) tests for significance between the pre- and post-legislative periods. Furthermore, in a few cases, we use difference-in-differences estimation by comparing the evolution of the EU 'treated' countries relative to other similar but 'untreated' countries, before and after the 2004 revision of the general pharmaceutical legislation. More detailed methodology is provided where indicators are presented and data sources are available in Annex A.

1.1 INDUSTRIAL & ECONOMIC COMPETITIVENESS INDICATORS

The table below and in each of the following sections provide an overview of indicators analysed.

Indicator name	Indicator description
	International indicators:
IEC-1	Number of EU-origin medicines approved in the EU
IEC-2	Number of USA-origin medicines approved in the USA; Number of Japan-origin medicines approved in Japan; Number of Switzerland-origin medicines approved in Switzerland
IEC-3	Number of EU-origin medicines approved in one or more non-EU countries
IEC-4	Number of USA-origin medicines approved in the EU; Number of Japan-origin medicines approved in the EU; Number of Switzerland-origin medicines approved in the EU
IEC-5	Value of medicine exports EU to USA and USA to EU; Value of medicines exports EU to Japan and Japan to EU; Value of medicine exports EU to Switzerland and Switzerland to EU
IEC-6	Number of clinical trials performed in different geographies
	Internal EU indicators:
IEC-7	Employment in the pharmaceutical industry
IEC-8	GVA contribution of the pharmaceutical industry
IEC-9	Number of clinical trials conducted
IEC-10	Revenue generated by pharma companies
	Profitability of the sector:
IEC-11	Gross profit
	Additional IEC indicators:
IEC-12	Volumes of EU import/export of APIs, vaccines, finished pharmaceutical products and antibiotics
IEC-13	Values of EU import/export of APIs, vaccines, finished pharmaceutical products and antibiotics

IEC-1-4: Indicator definition and relevance with respect to the evaluation

Industrial and economic competitive indicators 1-4 are all related, measuring approvals of medicinal products with different geographic origins in different markets of interest.

If we consider competitiveness to mean the ability of a country or region to create welfare, taking into account the institutions, policies, and other factors which determine the level of productivity of a country or region, it is the intention of the IEC-1-4 indicators to measure changes in the ultimate output (productivity) of clinical research in the pharmaceutical industry, namely approved medicinal products both pre and post the implementation of the general pharmaceutical legislation. These approved products provide increased welfare in countries where they are approved, so the aim was to observe if the companies headquartered in the EU were able to be more productive (in terms of numbers of medicines approved) then competitors headquartered in

comparator countries, namely the USA, Japan, and Switzerland, which were assumed not to be influenced by the implementation of the general pharmaceutical legislation. In order to control for both the country of origin of the medicinal products (as defined by developer headquartered country) and for the region of approval, approvals of medicines with EU, USA, Japan, or Switzerland origin were compared in their respective home markets and the EU.

Methodology

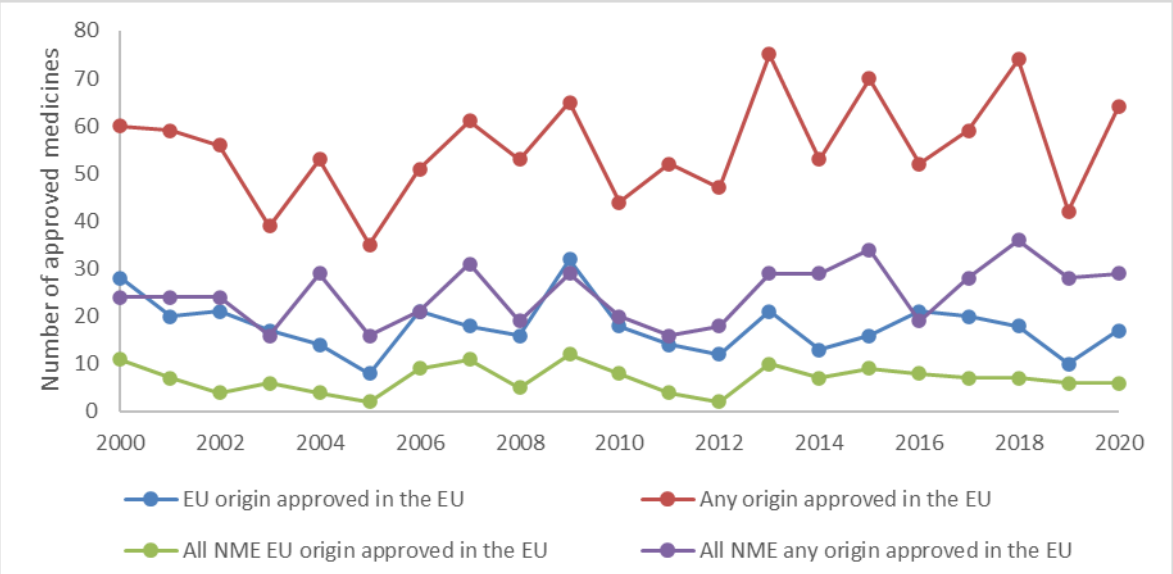
Throughout, all drug approval data are based on data contained within Pharmaprojects and Biomedtracker as of August 2021. The base data set for IEC-1-4 contained 4,981 products with a known approval date anywhere in the world. The approval year was set as first approval only; the number and dates of subsequent approvals relating to indication expansion were not counted. Therefore, in the case of approvals in the EU, no distinction is or can be made between drugs approved via the centralised or decentralised procedures using data from Pharmaprojects. Furthermore, all member states currently in the EU plus the UK were treated as having always been part of the EU for the entire analysis period. The scope of Pharmaprojects is also limited in that while the majority of medicinal products in development are covered, including biosimilars and reformulations relating to fixed dose combinations and route of administration reformulations by originator companies, approvals of generics or drug combinations are not recorded. The origin of the medical product was set by the HQ country of the originator company as recorded in Pharmaprojects. New molecular entity (NME) status as a definition of novel drug approvals was set by determining if products were recorded in Pharmaprojects as new chemical entities (NCEs) or new biologics (i.e., not recorded as a biosimilar or other generic). Pre and post refer to the analysis period before (pre defined as 2000-2004) or after (post defined as 2007-2020) the implementation of the general pharmaceutical legislation. Mean approvals per year and standard deviations were calculated for both the pre and post periods. Shapiro-Wilk tests were conducted to check data distribution prior to parametric (Welch's t-test) or non-parametric (Mann-Whitney U test) tests for significance between the pre and post groups. No post hoc or comparative analysis between indicators has been conducted. For all analyses, if the number of observations (in this case number of approved products) in an analysis period was less than 30, no statistical testing was performed or reported.

IEC-1: Number of EU-origin medicines approved in the EU

IEC-1 investigated approvals of EU-origin medicines in the EU in time periods both pre and post the implementation of the 2004 revision of the general pharmaceutical legislation. The number of approved products (via any authorisation route) were counted in each year between 2000 and 2020. Top level results comparing EU-origin medicines and medicines of any origin, split by new active substance status, are shown in Figure and Table IEC-1. While the average number of EU-origin medicines approved in the EU decreased in the post period, the difference was not statistically significant.[1] Analysis of the NME subset demonstrated that the average number of novel EU-origin medicines increased in the post period, but again the difference was not statistically significant. If the region of origin of the medicines is ignored, approvals for all products in the NME subset were shown to increase in the post period, but the difference was not statistically significant.

[1] Throughout this document, we show statistically significant differences between the pre and post periods by using **bold** p-value numbers in the analysis tables.

Figure IEC-1: EU-origin medicines approved in the EU and any origin medicines approved in the EU, split by all medicinal products or new active substances only.



Source: Pharmaprojects 2000-2020.

Table IEC-1 Descriptive statistics for EU-origin medicines approved in the EU and any origin medicines approved in the EU, split by all medicinal products or new active substances only

New molecular entity	Origin of medicine	Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH	N number	WELCH'S T-TEST (P-value)
All	EU	EU	Pre	18.429	5.827	12.601	24.256	100	0.759
All	EU	EU	Post	17.571	5.300	12.271	22.872	246	
All	All	EU	Pre	50.429	9.037	41.391	59.466	267	0.153
All	All	EU	Post	57.929	10.629	47.299	68.558	811	
New molecular entity	EU	EU	Pre	6.143	2.900	3.243	9.043	32	0.549
New molecular entity	EU	EU	Post	7.000	2.481	4.519	9.481	102	
New molecular entity	All	EU	Pre	22.000	4.375	17.625	26.375	117	0.164
New molecular entity	All	EU	Post	25.692	6.231	19.461	31.924	365	

Source: Pharmaprojects (2021) and Biomedtracker (2021). New active substance status was set by determining if products were recorded in Pharmaprojects as new molecular entities or new biologics (i.e., not recorded as a generic or a biosimilar). Mean approvals per year and standard deviations were calculated for both the pre and post periods. Shapiro-Wilk tests were conducted to check data distribution prior to parametric (Welch's t-test) tests for significance between the pre and post groups. Significant differences between the pre and post periods are highlighted in bold.

The data contained in Pharmaprojects facilitated the investigation of IEC-1 in more detail, both by therapy area and modality. The splits by therapy area for EU-origin medicines approved in the EU are shown in Table IEC1.2. In the post period, more oncology products were approved per year than in the pre period compared to the other therapy areas. No differences were observed for any other therapy area. In all cases, n

numbers were not sufficient for tests for statistical significance between the pre and post periods.

Table IEC1.2: Descriptive statistics for EU-origin medicines approved in the EU, split by therapy area

Therapy area	Origin of medicine	Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH
Autoimmune/Inflammation	EU	EU	Pre	3.571	1.498	2.073	5.070
Autoimmune/Inflammation	EU	EU	Post	2.857	1.542	1.315	4.399
Cardiovascular	EU	EU	Pre	2.286	1.750	0.536	4.035
Cardiovascular	EU	EU	Post	2.071	0.973	1.098	3.044
CNS	EU	EU	Pre	2.429	1.591	0.838	4.019
CNS	EU	EU	Post	2.786	2.162	0.624	4.948
Genitourinary	EU	EU	Pre	0.429	0.728	-0.300	1.157
Genitourinary	EU	EU	Post	0.714	0.738	-0.024	1.452
Infectious Disease	EU	EU	Pre	1.857	0.990	0.867	2.847
Infectious Disease	EU	EU	Post	1.143	1.406	-0.263	2.549
Metabolic/Endocrinology	EU	EU	Pre	3.857	1.959	1.898	5.816
Metabolic/Endocrinology	EU	EU	Post	3.214	1.961	1.253	5.175
Oncology	EU	EU	Pre	1.429	0.728	0.700	2.157
Oncology	EU	EU	Post	2.286	0.923	1.363	3.209
Ophthalmology	EU	EU	Pre	0.000	0.000	0.000	0.000
Ophthalmology	EU	EU	Post	0.214	0.421	-0.207	0.636
Vaccines	EU	EU	Pre	1.429	1.050	0.379	2.478
Vaccines	EU	EU	Post	1.786	2.044	-0.258	3.830

Source: Pharmaprojects (2021) and Biomedtracker (2021). New active substance status was set by determining if products were recorded in Pharmaprojects as new molecular entities or new biologics (i.e., not recorded as a generic or biosimilar). Mean approvals per year and standard deviations were calculated for both the pre and post periods.

Splits by modality are shown in Table IEC1. 3. In the post period, more antibody based products were approved than in the pre period. There were no differences observed related to any other modality investigated. Except for small molecules, n numbers were not sufficient in the pre analysis periods for tests for statistical significance between the pre and post periods, so such tests were not conducted.

Table IEC1. 3: Descriptive statistics for EU-origin medicines approved in the EU, split by modality

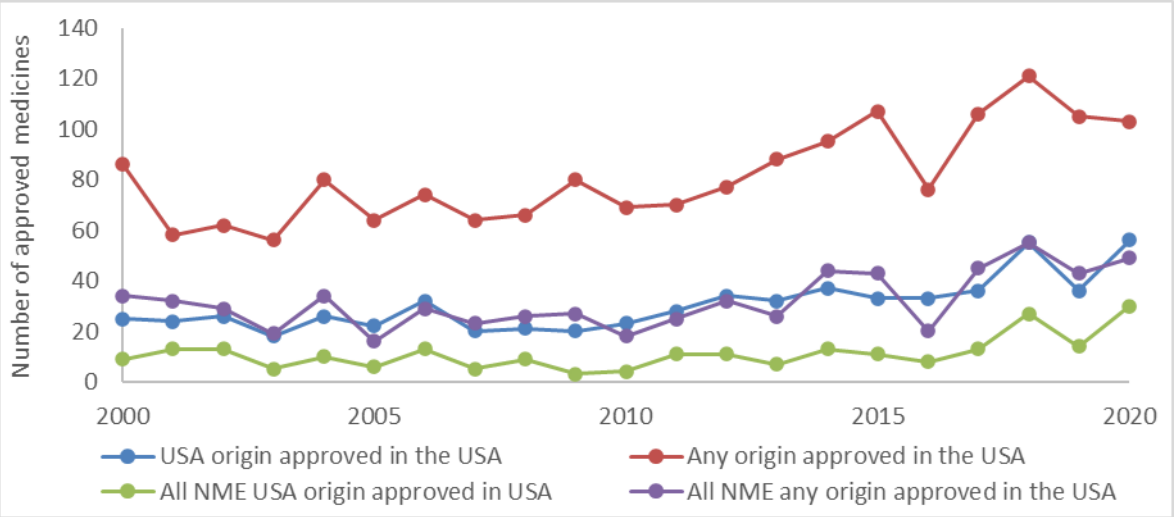
Modality	Origin of medicine	Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH
Small molecule	EU	EU	Pre	13.43	4.30	9.12	17.73
Small molecule	EU	EU	Post	10.79	4.10	6.69	14.88
Antibody	EU	EU	Pre	0.29	0.45	-0.17	0.74
Antibody	EU	EU	Post	1.36	1.19	0.17	2.54
Cell therapy	EU	EU	Pre	0.00	0.00	0.00	0.00
Cell therapy	EU	EU	Post	0.14	0.36	-0.22	0.50
Gene therapy	EU	EU	Pre	0.14	0.35	-0.21	0.49
Gene therapy	EU	EU	Post	0.14	0.36	-0.22	0.50
RNA	EU	EU	Pre	0.00	0.00	0.00	0.00
RNA	EU	EU	Post	0.07	0.27	-0.20	0.34
Peptide	EU	EU	Pre	0.14	0.35	-0.21	0.49
Peptide	EU	EU	Post	0.00	0.00	0.00	0.00
Fusion protein	EU	EU	Pre	0.00	0.00	0.00	0.00
Fusion protein	EU	EU	Post	0.07	0.27	-0.20	0.34
Other biological	EU	EU	Pre	4.57	1.99	2.58	6.56
Other biological	EU	EU	Post	5.07	2.60	2.47	7.67

Source: Pharmaprojects (2021) and Biomedtracker (2021). New active substance status was set by determining if products were recorded in Pharmaprojects as new molecular entities or new biologics (i.e., not recorded as a generic or a biosimilar). Mean approvals per year and standard deviations were calculated for both the pre and post periods.

IEC-2: number of USA-origin medicines approved in the USA, Japan-origin medicines approved in Japan, and Switzerland-origin medicines approved in Switzerland

IEC-2 investigated approvals of USA-origin medicines in the USA, Japan-origin medicines in Japan, and Switzerland-origin medicines in Switzerland in time periods both pre and post the implementation of the 2004 revision of the general pharmaceutical legislation. Top level results comparing USA-origin medicines and medicines of any origin, split by NME status, are shown in Figure and Table IEC2.1. The average number of USA-origin medicines approved in the USA was found to significantly increase in the post period, as did the number of medicines of any origin. However, the analysis of the subset demonstrated that while the average number of novel USA-origin medicines increased in the post period, the difference was not statistically significant. As with the EU, if the origin of the medicines is ignored, approvals for all products in the NME subset were shown to increase in the post period, but the difference was not statistically significant.

Figure IEC2.1: USA-origin medicines approved in the USA and any origin medicines approved in the USA, split by all medicinal products or new molecular entity only.



Source: Pharmaprojects 2000-2020.

Table IEC2.1: Descriptive statistics for USA-origin medicines approved in the USA and any origin medicines approved in the USA, split by all medicinal products or new molecular entity only

New molecular entity	Origin of medicine	Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH	N number	WELCH'S T-TEST (P-value)
All	USA	USA	Pre	24.71	3.95	20.76	28.67	119	**0.015**
All	USA	USA	Post	33.14	10.63	22.51	43.78	464	
All	All	USA	Pre	68.57	10.68	57.90	79.25	342	**0.006**
All	All	USA	Post	87.64	17.11	70.53	104.76	1,227	
New molecular entity	USA	USA	Pre	9.86	3.14	6.72	12.99	50	0.333
New molecular entity	USA	USA	Post	12.38	7.60	4.78	19.99	166	
New molecular entity	All	USA	Pre	27.57	6.69	20.88	34.27	148	0.110
New molecular entity	All	USA	Post	34.85	11.61	23.23	46.46	476	

Source: Pharmaprojects (2021) and Biomedtracker (2021). New active substance status was set by determining if products were recorded in Pharmaprojects as new molecular entities or new biologics (i.e., not recorded as a generic or a biosimilar). Mean approvals per year and standard deviations were calculated for both the pre and post periods. Shapiro-Wilk tests were conducted to check data distribution prior to parametric (Welch's t-test) tests for significance between the pre and post groups. Significant differences between the pre and post periods are highlighted in bold.

Regarding therapy area and modality splits for USA-origin medicines approved in the USA, no differences relating to therapy area were observed (Table IEC2.2). Regarding modality, increases in the number of small molecule, antibody, and RNA drugs were observed in the post period compared to the pre period (Table IEC2.3). For the RNA drugs, the number involved is very small (0 in the pre period and 9 in the post period). N numbers were not sufficient for statistical comparisons between the pre and post periods.

Table IEC2.2: Descriptive statistics for USA-origin medicines approved in the USA, split by therapy area

Therapy area	Origin of medicine	Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH
Autoimmune/Inflammation	USA	USA	Pre	4.14	1.88	2.26	6.03
Autoimmune/Inflammation	USA	USA	Post	5.00	2.09	2.91	7.09
Cardiovascular	USA	USA	Pre	2.14	1.25	0.90	3.39
Cardiovascular	USA	USA	Post	3.00	2.13	0.87	5.13
CNS	USA	USA	Pre	4.86	2.03	2.83	6.89
CNS	USA	USA	Post	6.43	2.30	4.13	8.73
Genitourinary	USA	USA	Pre	1.14	0.83	0.31	1.98
Genitourinary	USA	USA	Post	1.57	1.22	0.36	2.79
Infectious Disease	USA	USA	Pre	3.14	1.64	1.50	4.78
Infectious Disease	USA	USA	Post	3.93	3.16	0.77	7.09
Metabolic/Endocrinology	USA	USA	Pre	3.71	2.05	1.66	5.76
Metabolic/Endocrinology	USA	USA	Post	3.86	2.48	1.38	6.33
Oncology	USA	USA	Pre	2.71	1.67	1.05	4.38
Oncology	USA	USA	Post	5.93	5.20	0.73	11.13
Ophthalmology	USA	USA	Pre	0.57	0.49	0.08	1.07
Ophthalmology	USA	USA	Post	0.93	0.62	0.31	1.54
Vaccines	USA	USA	Pre	1.00	0.76	0.24	1.76
Vaccines	USA	USA	Post	0.64	0.92	-0.28	1.57

Source: Pharmaprojects (2021) and Biomedtracker (2021). New active substance status was set by determining if products were recorded in Pharmaprojects as new molecular entities or new biologics (i.e., not recorded as a generic or a biosimilar). Mean approvals per year and standard deviations were calculated for both the pre and post periods.

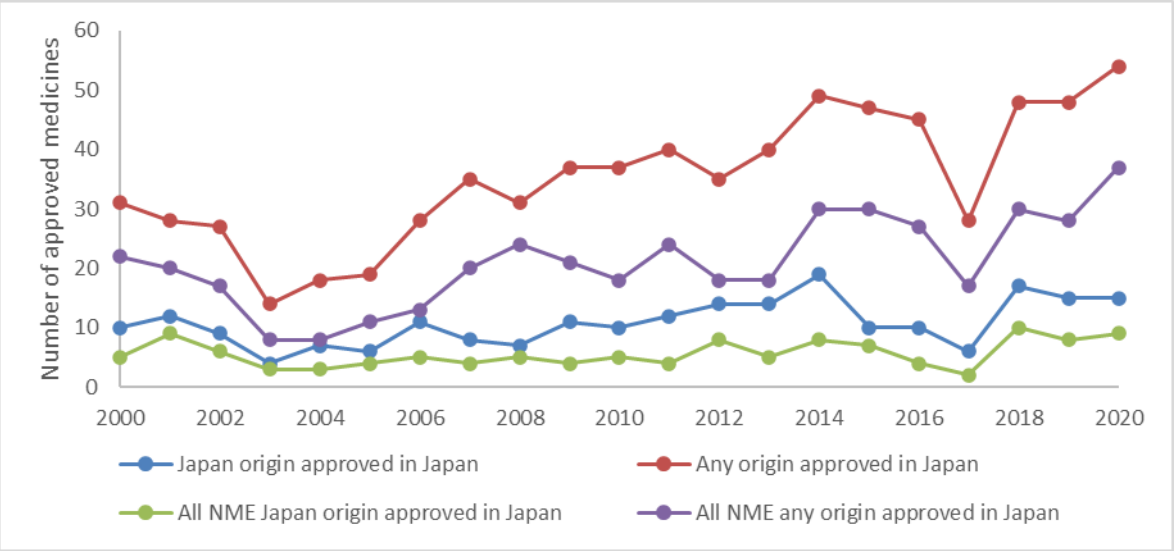
Table IEC2.3: Descriptive statistics for USA-origin medicines approved in the USA split by modality

Modality	Origin of medicine	Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH
Small molecule	USA	USA	Pre	17.86	3.87	13.99	21.73
Small molecule	USA	USA	Post	23.71	7.60	16.11	31.32
Antibody	USA	USA	Pre	0.71	0.70	0.01	1.41
Antibody	USA	USA	Post	3.21	2.53	0.68	5.74
Cell therapy	USA	USA	Pre	0.29	0.45	-0.17	0.74
Cell therapy	USA	USA	Post	0.71	0.62	0.09	1.34
Gene therapy	USA	USA	Pre	0.14	0.35	-0.21	0.49
Gene therapy	USA	USA	Post	0.71	0.82	-0.11	1.54
RNA	USA	USA	Pre	0.00	0.00	0.00	0.00
RNA	USA	USA	Post	0.64	0.91	-0.27	1.55
Peptide	USA	USA	Pre	0.00	0.00	0.00	0.00
Peptide	USA	USA	Post	0.14	0.36	-0.22	0.50
Fusion protein	USA	USA	Pre	0.14	0.35	-0.21	0.49
Fusion protein	USA	USA	Post	0.50	0.75	-0.25	1.25
Other biological	USA	USA	Pre	5.71	1.75	3.96	7.46
Other biological	USA	USA	Post	4.43	1.60	2.83	6.03

Source: Pharmaprojects (2021) and Biomedtracker (2021). New active substance status was set by determining if products were recorded in Pharmaprojects as new molecular entities or new biologics (i.e., not recorded as a generic or a biosimilar). Mean approvals per year and standard deviations were calculated for both the pre and post periods.

Top level results comparing Japan-origin medicines and medicines of any origin, split by NME status, are shown in Figure IEC2.2 and Table IEC2.4. The average number of Japan-origin medicines approved in Japan was found to significantly increase in the post period, as was the number of medicines of any origin. However, the analysis of the NME subset demonstrated that while the average number of novel Japan-origin medicines increased in the post period, no difference was observed and n numbers were insufficient for statistical analysis. In contrast to the EU and the USA, if the origin of the medicines is ignored, approvals for all products in the NME subset were shown to significantly increase in the post period compared to the pre period.

Figure IEC2.2: Japan-origin medicines approved in Japan and any origin medicines approved in Japan split by all medicinal products or new molecular entities only.



Source: Pharmaprojects 2000-2020.

Table IEC2.4 Descriptive statistics for Japan-origin medicines approved in Japan and any origin medicines approved in Japan, split by all medicinal products or new molecular entities only

New molecular entity	Origin of medicine	Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH	N number	WELCH'S T-TEST (P-value)
All	Japan	Japan	Pre	8.43	2.66	5.76	11.09	42	**0.021**
All	Japan	Japan	Post	12.00	3.65	8.35	15.65	168	
All	All	Japan	Pre	23.57	5.97	17.60	29.54	118	**0.001**
All	All	Japan	Post	41.00	7.44	33.56	48.44	574	
New molecular entity	Japan	Japan	Pre	5.00	1.93	3.07	6.93	26	Not determined
New molecular entity	Japan	Japan	Post	6.08	2.30	3.77	8.38	88	
New molecular entity	All	Japan	Pre	14.14	5.22	8.92	19.36	75	**0.002**
New molecular entity	All	Japan	Post	24.77	5.95	18.82	30.72	342	

Source: Pharmaprojects (2021) and Biomedtracker (2021). New active substance status was set by determining if products were recorded in Pharmaprojects as new molecular entities or new biologics (i.e., not recorded as a generic or a biosimilar). Mean approvals per year and standard deviations were calculated for both the pre and post periods. Shapiro-Wilk tests were conducted to check data distribution prior to parametric (Welch's t-test) tests for significance between the pre and post groups. Significant differences between the pre and post periods are highlighted in bold.

Regarding therapy area and modality splits for Japan-origin medicines approved in Japan, increases in approvals for central nervous system, metabolic/endocrinology, and oncology products were observed in the post period (Table IEC2.5). Regarding modalities, differences were observed with other biological products increasing in the post period compared to the pre period (Table IEC2.6). In other cases, the number of approvals was too low to perform statistical analysis.

Table IEC2.5 Descriptive statistics for Japan-origin medicines approved in Japan, split by therapy area

Therapy area	Origin of medicine	Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH
Autoimmune/Inflammation	Japan	Japan	Pre	2.29	2.43	-0.15	4.72
Autoimmune/Inflammation	Japan	Japan	Post	1.71	0.89	0.82	2.60
Cardiovascular	Japan	Japan	Pre	1.43	0.73	0.70	2.16
Cardiovascular	Japan	Japan	Post	1.50	1.50	0.00	3.00
CNS	Japan	Japan	Pre	0.57	0.49	0.08	1.07
CNS	Japan	Japan	Post	1.71	1.29	0.42	3.01
Genitourinary	Japan	Japan	Pre	0.57	0.73	-0.16	1.30
Genitourinary	Japan	Japan	Post	0.43	0.62	-0.20	1.05
Infectious Disease	Japan	Japan	Pre	1.29	1.03	0.26	2.32
Infectious Disease	Japan	Japan	Post	0.79	0.97	-0.19	1.76
Metabolic/Endocrinology	Japan	Japan	Pre	1.00	1.07	-0.07	2.07
Metabolic/Endocrinology	Japan	Japan	Post	2.86	1.07	1.79	3.93
Oncology	Japan	Japan	Pre	0.57	0.49	0.08	1.07
Oncology	Japan	Japan	Post	1.79	1.14	0.64	2.93
Ophthalmology	Japan	Japan	Pre	0.14	0.35	-0.21	0.49
Ophthalmology	Japan	Japan	Post	0.57	0.74	-0.17	1.31
Vaccines	Japan	Japan	Pre	0.29	0.70	-0.41	0.99
Vaccines	Japan	Japan	Post	0.43	0.62	-0.20	1.05

Source: Pharmaprojects (2021) and Biomedtracker (2021). Mean approvals per year and standard deviations were calculated for both the pre and post periods.

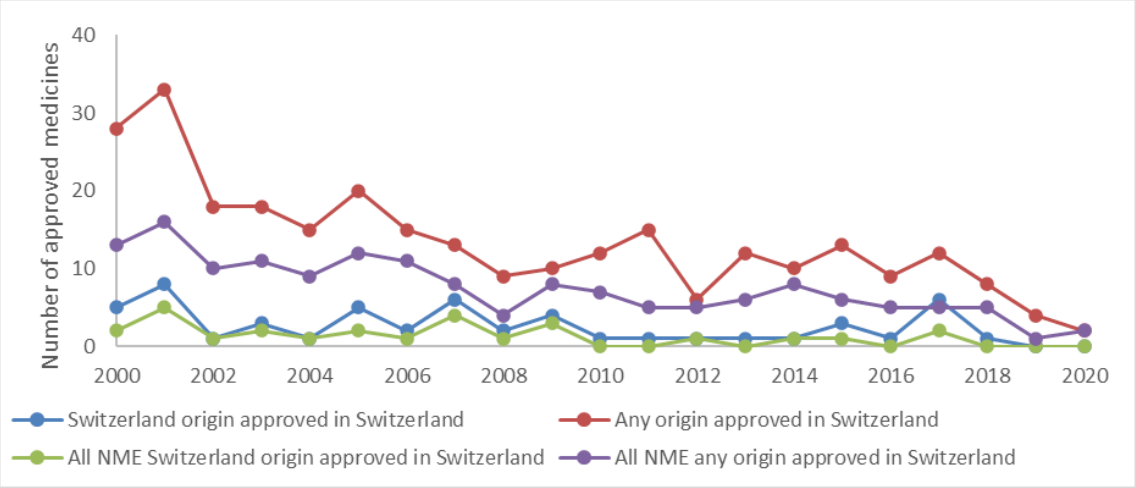
Table IEC2.6 Descriptive statistics for Japan-origin medicines approved in Japan, split by modality

Modality	Origin of medicine	Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH
Small molecule	Japan	Japan	Pre	7.71	2.05	5.66	9.76
Small molecule	Japan	Japan	Post	9.57	3.02	6.55	12.60
Antibody	Japan	Japan	Pre	0.14	0.35	-0.21	0.49
Antibody	Japan	Japan	Post	0.43	0.63	-0.21	1.06
Cell therapy	Japan	Japan	Pre	0.00	0.00	0.00	0.00
Cell therapy	Japan	Japan	Post	0.21	0.42	-0.21	0.64
Gene therapy	Japan	Japan	Pre	0.00	0.00	0.00	0.00
Gene therapy	Japan	Japan	Post	0.14	0.36	-0.22	0.50
RNA	Japan	Japan	Pre	0.00	0.00	0.00	0.00
RNA	Japan	Japan	Post	0.07	0.27	-0.20	0.34
Peptide	Japan	Japan	Pre	0.00	0.00	0.00	0.00
Peptide	Japan	Japan	Post	0.00	0.00	0.00	0.00
Fusion protein	Japan	Japan	Pre	0.00	0.00	0.00	0.00
Fusion protein	Japan	Japan	Post	0.00	0.00	0.00	0.00
Other biological	Japan	Japan	Pre	0.57	0.73	-0.16	1.30
Other biological	Japan	Japan	Post	1.71	1.00	0.71	2.72

Source: Pharmaprojects (2021) and Biomedtracker (2021). Mean approvals per year and standard deviations were calculated for both the pre and post periods.

Top level results comparing Switzerland-origin medicines and medicines of any origin, split by NME status, are shown in Figure IEC2.3 and Table IEC2.7. It should be noted that the n numbers in the Switzerland calculations are vastly reduced compared to the other analysis regions, as can be observed in the differences in the mean values for the pre and post periods, and they were not sufficient for statistical analysis. The average number of Switzerland-origin medicines approved in Switzerland was found to decrease in the post period. For the products of any origin, approvals were also shown to decrease in the post period compared to the pre period. The analysis of the NME subset demonstrated that the average number of novel Switzerland-origin medicines also decreased in the post period. In further contrast to the other analysis regions, if the origin of the medicines is ignored, approvals for all products in the NME subset were shown to decrease in the post period compared to the pre period.

Figure IEC2.3 Switzerland-origin medicines approved in Switzerland and any origin medicines approved in Switzerland split by all medicinal products or new molecular entities only.



Source: Pharmaprojects 2000-2020.

Table IEC2.7 Descriptive statistics for Switzerland-origin medicines approved in Switzerland and any origin medicines approved in Switzerland, split by all medicinal products or new molecular entities only

New molecular entity	Origin of medicine	Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH
All	Switzerland	Switzerland	Pre	2.71	1.83	0.88	4.54
All	Switzerland	Switzerland	Post	2.07	1.29	0.78	3.36
All	All	Switzerland	Pre	16.00	5.90	10.10	21.90
All	All	Switzerland	Post	7.50	2.53	4.97	10.03
New molecular entity	Switzerland	Switzerland	Pre	1.86	1.64	0.22	3.50
New molecular entity	Switzerland	Switzerland	Post	0.69	0.82	-0.13	1.51
New molecular entity	All	Switzerland	Pre	8.86	2.75	6.11	11.61
New molecular entity	All	Switzerland	Post	3.23	1.53	1.70	4.76

Source: Pharmaprojects (2021) and Biomedtracker (2021). New active substance status was set by determining if products were recorded in Pharmaprojects as new molecular entities or new biologics (i.e., not recorded as a generic or a biosimilar). Mean approvals per year and standard deviations were calculated for both the pre and post periods.

Regarding therapy area and modality splits for Switzerland-origin medicines approved in Switzerland, no significant differences were observed for either therapy area (Table IEC2.8) or modality (Table IEC2.9) In other cases, n numbers were not sufficient to report the results of statistical tests for significance.

Table IEC2.8 Descriptive statistics for Switzerland-origin medicines approved in Switzerland split by therapy area

Therapy area	Origin of medicine	Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH
Autoimmune/Inflammation	Switzerland	Switzerland	Pre	1.43	1.59	-0.16	3.02
Autoimmune/Inflammation	Switzerland	Switzerland	Post	0.29	0.61	-0.32	0.89
Cardiovascular	Switzerland	Switzerland	Pre	0.43	0.49	-0.07	0.92
Cardiovascular	Switzerland	Switzerland	Post	0.36	0.42	-0.06	0.78
CNS	Switzerland	Switzerland	Pre	0.00	0.00	0.00	0.00
CNS	Switzerland	Switzerland	Post	0.21	0.58	-0.36	0.79
Genitourinary	Switzerland	Switzerland	Pre	0.14	0.35	-0.21	0.49
Genitourinary	Switzerland	Switzerland	Post	0.21	0.58	-0.36	0.79
Infectious Disease	Switzerland	Switzerland	Pre	0.29	0.45	-0.17	0.74
Infectious Disease	Switzerland	Switzerland	Post	0.29	0.58	-0.29	0.86
Metabolic/Endocrinology	Switzerland	Switzerland	Pre	0.43	0.49	-0.07	0.92
Metabolic/Endocrinology	Switzerland	Switzerland	Post	0.36	0.46	-0.10	0.82
Oncology	Switzerland	Switzerland	Pre	0.29	0.45	-0.17	0.74
Oncology	Switzerland	Switzerland	Post	0.36	0.61	-0.25	0.96
Ophthalmology	Switzerland	Switzerland	Pre	0.29	0.45	-0.17	0.74
Ophthalmology	Switzerland	Switzerland	Post	0.00	0.00	0.00	0.00
Vaccines	Switzerland	Switzerland	Pre	0.00	0.00	0.00	0.00
Vaccines	Switzerland	Switzerland	Post	0.00	0.00	0.00	0.00

Source: Pharmaprojects (2021) and Biomedtracker (2021). Mean approvals per year and standard deviations were calculated for both the pre and post periods.

Table IEC2.9 Descriptive statistics for Switzerland-origin medicines approved in Switzerland split by modality

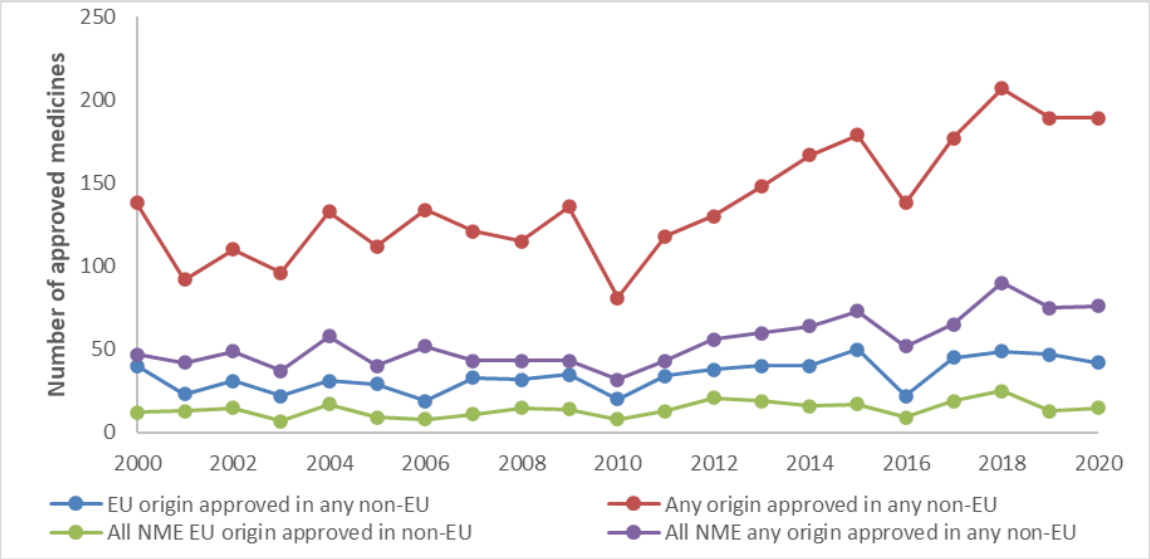
Modality	Origin of medicine	Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH
Small molecule	EU	EU	Pre	2.14	1.81	0.34	3.95
Small molecule	EU	EU	Post	1.00	0.89	0.11	1.89
Antibody	EU	EU	Pre	0.29	0.45	-0.17	0.74
Antibody	EU	EU	Post	0.43	0.75	-0.32	1.17
Cell therapy	EU	EU	Pre	0.00	0.00	0.00	0.00
Cell therapy	EU	EU	Post	0.00	0.00	0.00	0.00
Gene therapy	EU	EU	Pre	0.00	0.00	0.00	0.00
Gene therapy	EU	EU	Post	0.07	0.27	-0.20	0.34
RNA	EU	EU	Pre	0.00	0.00	0.00	0.00
RNA	EU	EU	Post	0.00	0.00	0.00	0.00
Peptide	EU	EU	Pre	0.00	0.00	0.00	0.00
Peptide	EU	EU	Post	0.00	0.00	0.00	0.00
Fusion protein	EU	EU	Pre	0.00	0.00	0.00	0.00
Fusion protein	EU	EU	Post	0.00	0.00	0.00	0.00
Other biological	EU	EU	Pre	0.29	0.70	-0.41	0.99
Other biological	EU	EU	Post	0.64	1.08	-0.43	1.72

Source: Pharmaprojects (2021) and Biomedtracker (2021). Mean approvals per year and standard deviations were calculated for both the pre and post periods.

IEC-3: Number of EU-origin medicines approved in one or more non-EU countries

IEC-3 investigated approvals of EU-origin medicines in one or more non-EU countries in time periods both pre and post the implementation of the 2004 revision of the general pharmaceutical legislation. Top level results comparing EU-origin medicines and medicines of any origin, split by NME, are shown in Figure IEC-3.1 and Table IEC-3.1. The average number of EU-origin medicines approved in one or more non-EU countries was found to increase in the post period, but the difference was not significant. The number of medicines of any origin approved in one or more non-EU countries increased significantly in the post period. The analysis of the NME subset demonstrated that both the average number of novel EU-origin medicines and any origin medicines increased significantly in the post period. In the pre period, approximately 70% of medicines of EU origin were found to be approved both in the EU and outside the EU; this rose to almost 80% in the post period.

Figure IEC-3.1 EU-origin medicines approved in one or more non-EU countries and any origin medicines approved in one or more non-EU countries split by all medicinal products or new molecular entities only.



Source: Pharmaprojects 2000-2020.

Table IEC-3.1 Descriptive statistics for EU-origin medicines approved in one or more non-EU countries, split by all medicinal products or new molecular entities only

New molecular entity	Origin of medicine	Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH	N number	WELCH'S T-TEST (P-value)
All	EU	Non-EU	Pre	27.86	6.60	21.26	34.46	147	0.222
All	EU	Non-EU	Post	37.64	9.03	28.61	46.67	527	
All	All	Non-EU	Pre	116.43	17.42	99.01	133.85	569	**0.010**
All	All	Non-EU	Post	149.64	34.93	114.71	184.57	2095	
New molecular entity	EU	Non-EU	Pre	11.57	3.46	8.11	15.03	64	**0.048**
New molecular entity	EU	Non-EU	Post	15.69	4.48	11.21	20.17	215	
New molecular entity	All	Non-EU	Pre	46.43	6.78	39.65	53.21	233	**0.027**
New molecular entity	All	Non-EU	Post	59.38	15.97	43.41	75.36	815	

Source: Pharmaprojects (2021) and Biomedtracker (2021). New active substance status was set by determining if products were recorded in Pharmaprojects as new molecular entities or new biologics (i.e., not recorded as a generic or a biosimilar). Mean approvals per year and standard deviations were calculated for both the pre and post periods. Shapiro-Wilk tests were conducted to check data distribution prior to parametric (Welch's t-test) tests for significance between the pre and post groups. Significant differences between the pre and post periods are highlighted in bold.

Regarding therapy area and modality splits for EU-origin medicines approved in one or more non-EU countries, observable increases were seen for CNS and genitourinary in the post period compared to the pre period (Table IEC-3.2). Regarding modalities, observable increases were seen relating to approvals for small molecules, antibodies, and gene therapies (Table IEC-3.3).

Table IEC-3.2 Descriptive statistics for EU-origin medicines approved in one or more non-EU countries split by therapy area

Therapy area	Origin of medicine	Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH
Autoimmune/Inflammation	EU	Non-EU	Pre	4.43	3.54	0.89	7.97
Autoimmune/Inflammation	EU	Non-EU	Post	8.29	3.45	4.83	11.74
Cardiovascular	EU	Non-EU	Pre	5.29	2.66	2.63	7.94
Cardiovascular	EU	Non-EU	Post	4.79	2.20	2.59	6.99
CNS	EU	Non-EU	Pre	3.57	0.73	2.84	4.30
CNS	EU	Non-EU	Post	5.50	2.06	3.44	7.56
Genitourinary	EU	Non-EU	Pre	0.71	0.45	0.26	1.17
Genitourinary	EU	Non-EU	Post	1.64	1.31	0.33	2.95
Infectious Disease	EU	Non-EU	Pre	3.14	1.25	1.90	4.39
Infectious Disease	EU	Non-EU	Post	3.64	2.58	1.07	6.22
Metabolic/Endocrinology	EU	Non-EU	Pre	3.57	1.92	1.65	5.49
Metabolic/Endocrinology	EU	Non-EU	Post	5.57	2.87	2.70	8.44
Oncology	EU	Non-EU	Pre	3.00	1.69	1.31	4.69
Oncology	EU	Non-EU	Post	3.64	1.44	2.20	5.09
Ophthalmology	EU	Non-EU	Pre	0.14	0.35	-0.21	0.49
Ophthalmology	EU	Non-EU	Post	0.64	0.82	-0.18	1.46
Vaccines	EU	Non-EU	Pre	2.29	1.83	0.46	4.12
Vaccines	EU	Non-EU	Post	2.57	1.94	0.63	4.51

Source: Pharmaprojects (2021) and Biomedtracker (2021). New active substance status was set by determining if products were recorded in Pharmaprojects as new molecular entities or new biologics (i.e., not recorded as a generic or a biosimilar). Mean approvals per year and standard deviations were calculated for both the pre and post periods.

Table IEC-3.3 Descriptive statistics for EU-origin medicines approved in one or more non-EU countries split by modality

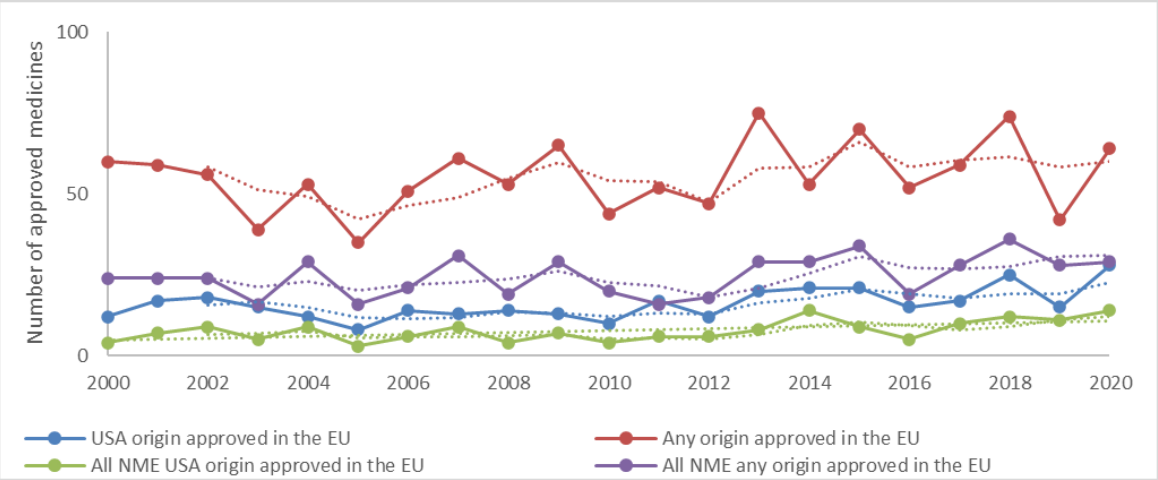
Modality	Origin of medicine	Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH
Small molecule	EU	Non-EU	Pre	20.43	4.66	15.77	25.08
Small molecule	EU	Non-EU	Post	26.86	6.80	20.06	33.66
Antibody	EU	Non-EU	Pre	0.43	0.49	-0.07	0.92
Antibody	EU	Non-EU	Post	1.64	1.31	0.33	2.95
Cell therapy	EU	Non-EU	Pre	0.00	0.00	0.00	0.00
Cell therapy	EU	Non-EU	Post	0.21	0.42	-0.21	0.64
Gene therapy	EU	Non-EU	Pre	0.00	0.00	0.00	0.00
Gene therapy	EU	Non-EU	Post	0.57	0.62	-0.05	1.20
RNA	EU	Non-EU	Pre	0.00	0.00	0.00	0.00
RNA	EU	Non-EU	Post	0.00	0.00	0.00	0.00
Peptide	EU	Non-EU	Pre	0.00	0.00	0.00	0.00
Peptide	EU	Non-EU	Post	0.07	0.27	-0.20	0.34
Fusion protein	EU	Non-EU	Pre	0.00	0.00	0.00	0.00
Fusion protein	EU	Non-EU	Post	0.07	0.27	-0.20	0.34
Other biological	EU	Non-EU	Pre	7.00	2.98	4.02	9.98
Other biological	EU	Non-EU	Post	8.79	3.62	5.17	12.41

Source: Pharmaprojects (2021) and Biomedtracker (2021).

IEC-4: number of USA-origin medicines approved in the EU; number of Japan-origin medicines approved in the EU; number of Switzerland-origin medicines approved in the EU

IEC-4 investigated approvals of USA-origin medicines in the EU, Japan-origin medicines in the EU, and Switzerland-origin medicines in the EU in time periods both pre and post the implementation of the 2004 revision of the general pharmaceutical legislation. Top level results comparing USA-origin medicines, split by NME status, are shown in Figure IEC-4.1 and Table IEC-4.1. For comparison, approval of medicines of any origin in the EU is shown. While in all cases the number of medicines approved was shown to increase in the post period compared to the pre period, differences were not significant.

Figure IEC-4.1 USA-origin medicines approved in the EU and any origin medicines approved in the EU split by all medicinal products or new molecular entities only.



Source: Pharmaprojects 2000-2020.

Table IEC-4.1 Descriptive statistics for USA-origin medicines approved in the EU, split by all medicinal products or new molecular entities only

New molecular entity	Origin of medicine	Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH	N number	WELCH'S T-TEST (P-value)
All	USA	EU	Pre	22.00	3.96	18.04	25.96	74	0.065
All	USA	EU	Post	25.93	9.84	16.09	35.76	241	
All	All	EU	Pre	50.43	9.04	41.39	59.47	267	0.153
All	All	EU	Post	57.93	10.63	47.30	68.56	811	
New molecular entity	USA	EU	Pre	8.00	3.51	4.49	11.51	34	0.097
New molecular entity	USA	EU	Post	9.31	2.70	6.61	12.01	119	
New molecular entity	All	EU	Pre	22.00	4.38	17.62	26.38	177	0.164
New molecular entity	All	EU	Post	25.69	6.23	19.46	31.92	365	

Source: Pharmaprojects (2021) and Biomedtracker (2021). New active substance status was set by determining if products were recorded in Pharmaprojects as new molecular entities or new biologics (i.e., not recorded as a generic or a biosimilar). Mean approvals per year and standard deviations were calculated for both the pre and post periods.

No differences were observed by therapy area (Table IEC-4.2), but for modality, approvals of antibody products and cell therapy products were shown to observably increase in the post period compared to the pre period (Table IEC-4.3).

Table IEC-4.2 Descriptive statistics for USA-origin medicines approved in the EU split by therapy area

Therapy area	Origin of medicine	Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH
Autoimmune/Inflammation	USA	EU	Pre	2.14	1.73	0.42	3.87
Autoimmune/Inflammation	USA	EU	Post	2.64	1.60	1.04	4.24
Cardiovascular	USA	EU	Pre	1.14	0.83	0.31	1.98
Cardiovascular	USA	EU	Post	1.36	1.69	-0.34	3.05
CNS	USA	EU	Pre	2.43	1.68	0.75	4.11
CNS	USA	EU	Post	2.07	1.23	0.84	3.30
Genitourinary	USA	EU	Pre	0.14	0.35	-0.21	0.49
Genitourinary	USA	EU	Post	0.29	0.61	-0.32	0.89
Infectious Disease	USA	EU	Pre	0.71	0.70	0.01	1.41
Infectious Disease	USA	EU	Post	0.36	0.62	-0.27	0.98
Metabolic/Endocrinology	USA	EU	Pre	1.71	1.16	0.55	2.87
Metabolic/Endocrinology	USA	EU	Post	3.29	2.04	1.24	5.33
Oncology	USA	EU	Pre	1.86	1.25	0.61	3.10
Oncology	USA	EU	Post	2.36	1.69	0.66	4.05
Ophthalmology	USA	EU	Pre	2.00	1.07	0.93	3.07
Ophthalmology	USA	EU	Post	3.64	2.52	1.12	6.17
Vaccines	USA	EU	Pre	0.57	0.73	-0.16	1.30
Vaccines	USA	EU	Post	0.50	0.75	-0.25	1.25

Source: Pharmaprojects (2021) and Biomedtracker (2021). Mean approvals per year and standard deviations were calculated for both the pre and post periods.

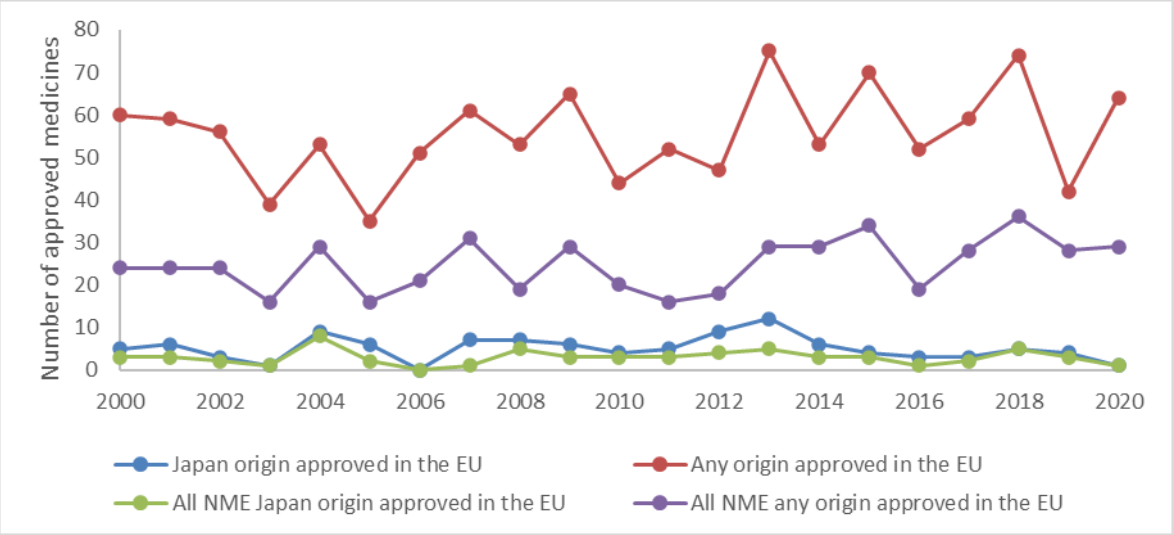
Table IEC-4.3 Descriptive statistics for USA-origin medicines approved in the EU split by modality

Modality	Origin of medicine	Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH
Small molecule	USA	EU	Pre	9.86	2.42	7.44	12.27
Small molecule	USA	EU	Post	10.64	3.03	7.62	13.67
Antibody	USA	EU	Pre	0.43	0.73	-0.30	1.16
Antibody	USA	EU	Post	2.57	2.43	0.14	5.00
Cell therapy	USA	EU	Pre	0.00	0.00	0.00	0.00
Cell therapy	USA	EU	Post	0.43	0.50	-0.07	0.93
Gene therapy	USA	EU	Pre	0.14	0.35	-0.21	0.49
Gene therapy	USA	EU	Post	0.36	0.62	-0.27	0.98
RNA	USA	EU	Pre	0.00	0.00	0.00	0.00
RNA	USA	EU	Post	0.50	0.93	-0.43	1.43
Peptide	USA	EU	Pre	0.00	0.00	0.00	0.00
Peptide	USA	EU	Post	0.14	0.36	-0.22	0.50
Fusion protein	USA	EU	Pre	0.14	0.35	-0.21	0.49
Fusion protein	USA	EU	Post	0.64	0.62	0.02	1.27
Other biological	USA	EU	Pre	3.29	1.03	2.26	4.32
Other biological	USA	EU	Post	2.43	1.15	1.28	3.57

Source: Pharmaprojects (2021) and Biomedtracker (2021). Mean approvals per year and standard deviations were calculated for both the pre and post periods.

Top level results comparing Japan-origin medicines, split by NME status, are shown in Figure IEC-4.2 and Table IEC-4.4. For comparison, the previously calculated all origin approval in the EU is shown. Similar to the USA-origin medicines, while in all cases the number of medicines approved was shown to increase in the post period compared to the pre period, differences were not significant or could not be determined statistically due to low numbers.

Figure IEC-4.2: Japan-origin medicines approved in the EU and any origin medicines approved in the EU split by all medicinal products or new molecular entities only.



Source: Pharmaprojects 2000-2020.

Table IEC-4.4 Descriptive statistics for Japan-origin medicines approved in the EU, split by all medicinal products or new molecular entities only

New molecular entity	**Origin of medicine**	**Region of approval**	**Pre or post**	**MEAN**	**STDEV**	**LOW**	**HIGH**	**N number**	**WELCH'S T-TEST (P-value)**
All	Japan	EU	Pre	4.29	2.91	1.37	7.20	24	Not determined
All	Japan	EU	Post	5.43	2.73	2.70	8.16	76	
All	All	EU	Pre	50.43	9.04	41.39	59.47	267	0.153
All	All	EU	Post	57.93	10.63	47.30	68.56	811	
New molecular entity	Japan	EU	Pre	2.71	2.37	0.34	5.09	17	Not determined
New molecular entity	Japan	EU	Post	3.15	1.29	1.86	4.45	42	
New molecular entity	All	EU	Pre	22.00	4.38	17.62	26.38	117	0.164
New molecular entity	All	EU	Post	25.69	6.23	19.46	31.92	365	

Source: Pharmaprojects (2021) and Biomedtracker (2021). New active substance status was set by determining if products were recorded in Pharmaprojects as new molecular entities or new biologics (i.e., not recorded as a generic or a biosimilar). Mean approvals per year and standard deviations were calculated for both the pre and post periods. Shapiro-Wilk tests were conducted to check data distribution prior to parametric (Welch's t-test) tests for significance between the pre and post groups. Significant differences between the pre and post periods are highlighted in bold.

Regarding therapy area splits, oncology products were shown to observably increase in the post period compared to the pre period (Table IEC-4.5). No differences were observed regarding modalities (Table IEC-4.6).

Table IEC-4.5 Descriptive statistics for USA-origin medicines approved in the USA and any origin medicines approved in the USA, split by therapy area

Therapy area	Origin of medicine	Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH
Autoimmune/Inflammation	Japan	EU	Pre	1.43	1.68	-0.25	3.11
Autoimmune/Inflammation	Japan	EU	Post	0.43	0.49	-0.06	0.92
Cardiovascular	Japan	EU	Pre	1.14	0.99	0.15	2.13
Cardiovascular	Japan	EU	Post	0.64	0.61	0.04	1.25
CNS	Japan	EU	Pre	0.29	0.45	-0.17	0.74
CNS	Japan	EU	Post	0.71	0.91	-0.20	1.62
Genitourinary	Japan	EU	Pre	0.29	0.45	-0.17	0.74
Genitourinary	Japan	EU	Post	0.21	0.42	-0.21	0.64
Infectious Disease	Japan	EU	Pre	0.00	0.00	0.00	0.00
Infectious Disease	Japan	EU	Post	0.43	0.62	-0.20	1.05
Metabolic/Endocrinology	Japan	EU	Pre	0.86	1.12	-0.27	1.98
Metabolic/Endocrinology	Japan	EU	Post	1.14	1.21	-0.06	2.35
Oncology	Japan	EU	Pre	0.29	0.45	-0.17	0.74
Oncology	Japan	EU	Post	1.36	0.84	0.52	2.19
Ophthalmology	Japan	EU	Pre	0.00	0.00	0.00	0.00
Ophthalmology	Japan	EU	Post	0.21	0.42	-0.21	0.64
Vaccines	Japan	EU	Pre	0.00	0.00	0.00	0.00
Vaccines	Japan	EU	Post	0.00	0.00	0.00	0.00

Source: Pharmaprojects (2021) and Biomedtracker (2021). Mean approvals per year and standard deviations were calculated for both the pre and post periods.

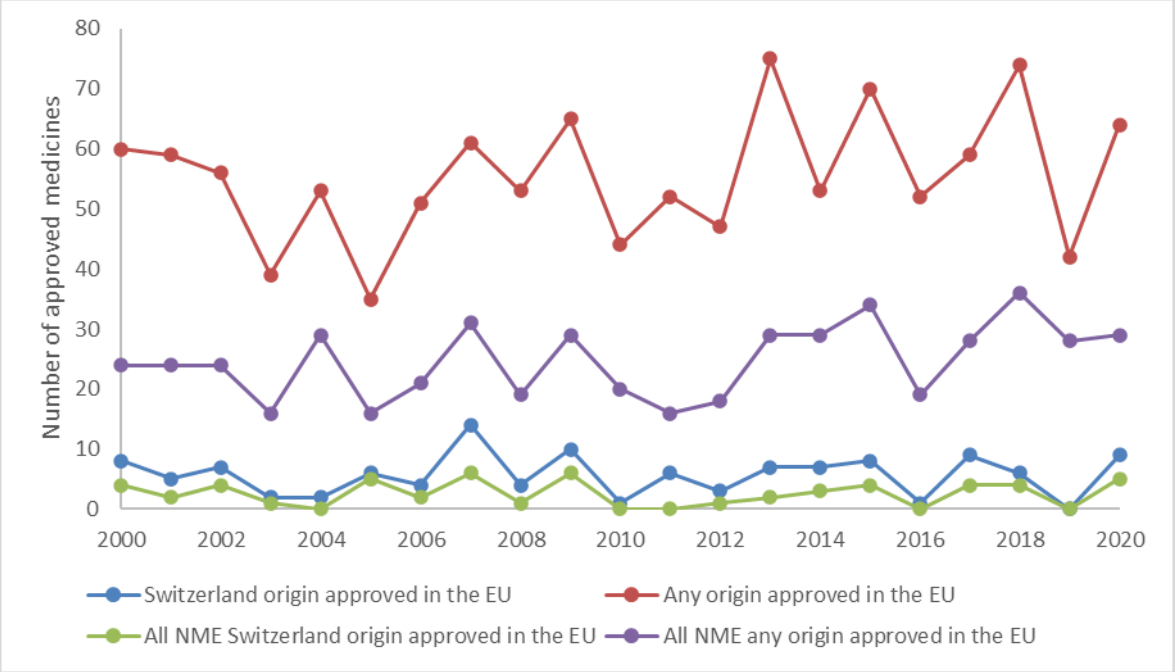
Table IEC-4.6 Descriptive statistics for Japan-origin medicines approved in the EU split by modality

Modality	Origin of medicine	Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH	WELCH'S T-TEST (P-value)
Small molecule	Japan	EU	Pre	3.86	2.85	1.01	6.71	0.637
Small molecule	Japan	EU	Post	4.57	2.73	1.84	7.31	
Antibody	Japan	EU	Pre	0.00	0.00	0.00	0.00	0.137
Antibody	Japan	EU	Post	0.36	0.84	-0.48	1.19	
Cell therapy	Japan	EU	Pre	0.00	0.00	0.00	0.00	0
Cell therapy	Japan	EU	Post	0.00	0.00	0.00	0.00	
Gene therapy	Japan	EU	Pre	0.00	0.00	0.00	0.00	0
Gene therapy	Japan	EU	Post	0.00	0.00	0.00	0.00	
RNA	Japan	EU	Pre	0.00	0.00	0.00	0.00	0
RNA	Japan	EU	Post	0.00	0.00	0.00	0.00	
Peptide	Japan	EU	Pre	0.00	0.00	0.00	0.00	0
Peptide	Japan	EU	Post	0.00	0.00	0.00	0.00	
Fusion protein	Japan	EU	Pre	0.00	0.00	0.00	0.00	0
Fusion protein	Japan	EU	Post	0.00	0.00	0.00	0.00	
Other biological	Japan	EU	Pre	0.43	0.49	-0.07	0.92	0.861
Other biological	Japan	EU	Post	0.50	0.49	0.01	0.99	

Source: Pharmaprojects (2021) and Biomedtracker (2021). Mean approvals per year and standard deviations were calculated for both the pre and post periods.

Top level results comparing Switzerland-origin medicines, split by NME status, are shown in Figure IEC-4.3 and Table IEC-4.7. For comparison, the previously calculated all origin approval in the EU is shown. Similar to the USA-origin medicines and Japan-origin medicines, in all cases, no differences were observed, but n numbers were not sufficient for statistical analysis.

Figure IEC-4.3 Switzerland-origin medicines approved in the EU and any origin medicines approved in the EU split by all medicinal products or new molecular entities only.



Source: Pharmaprojects 2000-2020.

Table IEC-4.7 Descriptive statistics for Switzerland-origin medicines approved in the EU, split by all medicinal products or new molecular entity only

New molecular entity	**Origin of medicine**	**Region of approval**	**Pre or post**	**MEAN**	**STDEV**	**LOW**	**HIGH**	**N number**	**WELCH'S T-TEST (P-value)**
All	Switzerland	EU	Pre	4.29	2.91	1.37	7.20	24	Not determined
All	Switzerland	EU	Post	5.43	2.73	2.70	8.16	85	
All	All	EU	Pre	50.43	9.04	41.39	59.47	267	0.153
All	All	EU	Post	57.93	10.63	47.30	68.56	811	
New molecular entity	Switzerland	EU	Pre	2.71	2.37	0.34	5.09	11	Not determined
New molecular entity	Switzerland	EU	Post	3.15	1.29	1.86	4.45	36	
New molecular entity	All	EU	Pre	22.00	4.38	17.62	26.38	117	0.164
New molecular entity	All	EU	Post	25.69	6.23	19.46	31.92	365	

Source: Pharmaprojects (2021) and Biomedtracker (2021). New active substance status was set by determining if products were recorded in Pharmaprojects as new molecular entities or new biologics (i.e., not recorded as a generic or a biosimilar). Mean approvals per year and standard deviations were calculated for both the pre and post periods. Shapiro-Wilk tests were conducted to check data distribution prior to parametric (Welch's t-test) tests for significance between the pre and post groups. Significant differences between the pre and post periods are highlighted in bold.

Regarding therapy area splits, similar to Japan-origin medicines, oncology products were shown to increase in the post period compared to the pre period (Table IEC-4.8), but no differences were observed regarding modalities (Table IEC-4.9).

Table IEC-4.8 Descriptive statistics for Switzerland-origin medicines approved in the EU split by therapy area

Therapy area	Origin of medicine	Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH
Autoimmune/Inflammation	Switzerland	EU	Pre	1.71	1.58	0.14	3.29
Autoimmune/Inflammation	Switzerland	EU	Post	1.07	1.07	0.00	2.14
Cardiovascular	Switzerland	EU	Pre	0.71	1.03	-0.32	1.74
Cardiovascular	Switzerland	EU	Post	0.93	0.70	0.23	1.63
CNS	Switzerland	EU	Pre	0.14	0.35	-0.21	0.49
CNS	Switzerland	EU	Post	0.29	0.42	-0.14	0.71
Genitourinary	Switzerland	EU	Pre	0.43	0.73	-0.30	1.16
Genitourinary	Switzerland	EU	Post	0.21	0.42	-0.21	0.64
Infectious Disease	Switzerland	EU	Pre	0.57	0.49	0.08	1.07
Infectious Disease	Switzerland	EU	Post	0.29	0.61	-0.32	0.89
Metabolic/Endocrinology	Switzerland	EU	Pre	0.43	0.73	-0.30	1.16
Metabolic/Endocrinology	Switzerland	EU	Post	0.79	0.62	0.16	1.41
Oncology	Switzerland	EU	Pre	0.71	0.45	0.26	1.17
Oncology	Switzerland	EU	Post	1.86	1.64	0.22	3.50
Ophthalmology	Switzerland	EU	Pre	0.29	0.45	-0.17	0.74
Ophthalmology	Switzerland	EU	Post	0.50	0.62	-0.12	1.12
Vaccines	Switzerland	EU	Pre	0.14	0.35	-0.21	0.49
Vaccines	Switzerland	EU	Post	0.00	0.00	0.00	0.00

Source: Pharmaprojects (2021) and Biomedtracker (2021). Mean approvals per year and standard deviations were calculated for both the pre and post periods.

Table IEC-4.9 Descriptive statistics for Switzerland-origin medicines approved in the EU, split by modality

Modality	Origin of medicine	Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH
Small molecule	Switzerland	EU	Pre	3.29	1.16	2.13	4.45
Small molecule	Switzerland	EU	Post	3.79	2.46	1.32	6.25
Antibody	Switzerland	EU	Pre	0.43	0.73	-0.30	1.16
Antibody	Switzerland	EU	Post	1.29	1.38	-0.09	2.67
Cell therapy	Switzerland	EU	Pre	0.00	0.00	0.00	0.00
Cell therapy	Switzerland	EU	Post	0.07	0.27	-0.20	0.34
Gene therapy	Switzerland	EU	Pre	0.14	0.35	-0.21	0.49
Gene therapy	Switzerland	EU	Post	0.29	0.72	-0.44	1.01
RNA	Switzerland	EU	Pre	0.00	0.00	0.00	0.00
RNA	Switzerland	EU	Post	0.00	0.00	0.00	0.00
Peptide	Switzerland	EU	Pre	0.00	0.00	0.00	0.00
Peptide	Switzerland	EU	Post	0.00	0.00	0.00	0.00
Fusion protein	Switzerland	EU	Pre	0.00	0.00	0.00	0.00
Fusion protein	Switzerland	EU	Post	0.07	0.27	-0.20	0.34
Other biological	Switzerland	EU	Pre	1.00	0.76	0.24	1.76
Other biological	Switzerland	EU	Post	0.86	0.61	0.25	1.46

Source: Pharmaprojects (2021) and Biomedtracker (2021). Mean approvals per year and standard deviations were calculated for both the pre and post periods.

Interpretation of possible causes for changes in IEC-1-4

In summary, there was no significant difference in the number of products approved in the EU that were developed by companies headquartered in the EU (EU-origin) following the implementation of the general pharmaceutical legislation compared to the period prior to implementation (IEC-1). However, it must be stated that no decline was observed, so companies were able to maintain the same level of productivity and welfare provision, despite well-known and widely discussed difficulties in successfully developing new medicinal products in the last 20 years. With that said, in the comparator countries, overall productivity for companies headquartered in the USA or Japan was seen to increase in their home markets as the number of drug approvals was demonstrated to increase (IEC-2). As a cross check, approvals of medicines of EU origin in countries outside the EU was investigated; again it was shown that companies headquartered in the EU were able to maintain, but not increase, productivity. This is evidence that it was not the approval procedure or at least any geographic factor that contributed to the overall numbers or change in numbers of approved products of EU-origin (IEC-3). The final set of observations was to look at the number of approved products in the EU from companies headquartered in the comparator regions. In all cases, productivity was maintained in the pre and post periods, demonstrating that the origin of the company was unlikely to be the driving factor behind the trends observed (IEC-4).

IEC-5.1: Value of medicine exports EU to Japan and Japan to EU

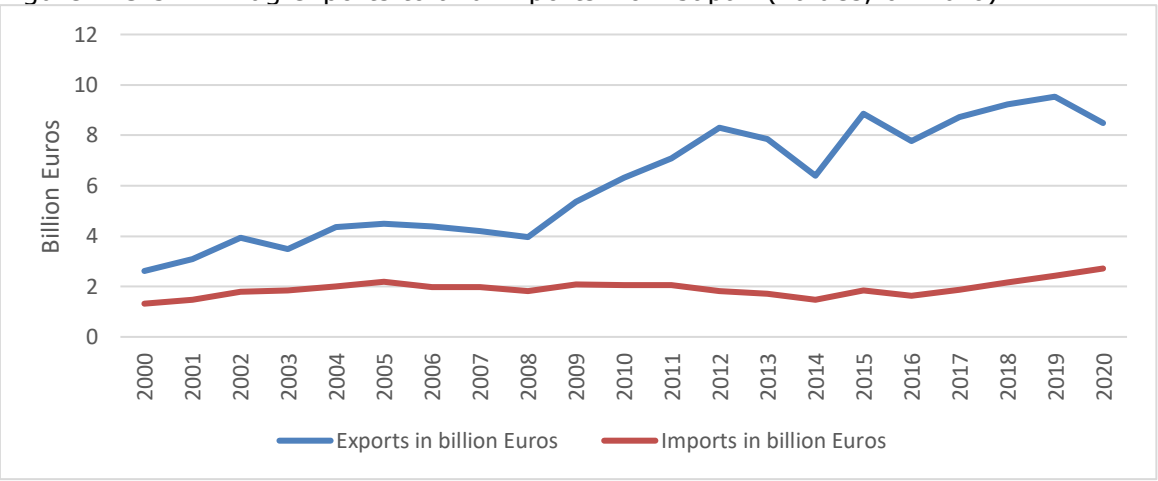
We have analysed the evolution of the EU's international trade in medicines, over the 20-year period from January 2000 to December 2020. We have run this analysis for several key trading partners, including Japan, Switzerland, and the US, each of which has been an important market for the EU pharmaceutical industry, as well as having its own strong domestic industry and regulatory frameworks. In each of these analyses,

we have used trade data from Eurostat. The definition of medicinal products includes the 126 product types listed in the Annex of the EFPIA-ECIPE report "Key Trade Data Points on the EU27 Pharmaceutical Supply Chain" published in July 2020. These 126 product types are categorised as Active Pharmaceutical Ingredients (APIs), Human Medicinal Products (HMPs), Finished Pharmaceutical Products (FPPs), Vaccines and Antibiotics (See the list of 126 product types in Annex B). The following graphs show medicinal products exports from EU27 countries and the UK (hereafter EU28) to Japan and Imports from Japan to EU28. For a breakdown of import/export trend figures for the various product types see additional IEC indicators IEC-12 and IEC-13 below.

The figures for the overall medicinal products show that exports from EU28 to Japan have grown strongly across the 20-year period, from around €2bn in 2000 to more than €8bn in 2020. The overall trend is characterised by several distinct phases, with exports remaining stable and close to €4bn a year during the period immediately following the introduction of the revised legislation (2004-2008), followed by double-digit annual growth in the period 2008-2012, reaching €8bn in 2012, notwithstanding the global financial crisis. Growth was more volatile in the subsequent 8-year period, with the value of exports in 2020 broadly equal to the value of exports in 2012. Interestingly, the EU-Japan Mutual Recognition Agreement, in force since 2004, does not seem to have had an immediate significant impact on EU28 exports of medicines to Japan, nor do the other elements of the EU's General Pharmaceutical legislation.

In comparison, EU28 imports from Japan have grown less strongly across the 20-year period, doubling in cash terms between 2000 and 2020, while EU exports to Japan had quadrupled in the same period. Moreover, the data show three phases, with clear growth in the 5-year period to 2005, followed by a weaker period, where imports were broadly flat or in decline, at around €2bn, across the 10-year period 2004-2014. In a third phase, the trade data show strong year-on-year growth in imports, from 2016 to 2020, outpacing EU exports.

Figure IEC-5.1: Drug exports to and imports from Japan (values, bn Euro)

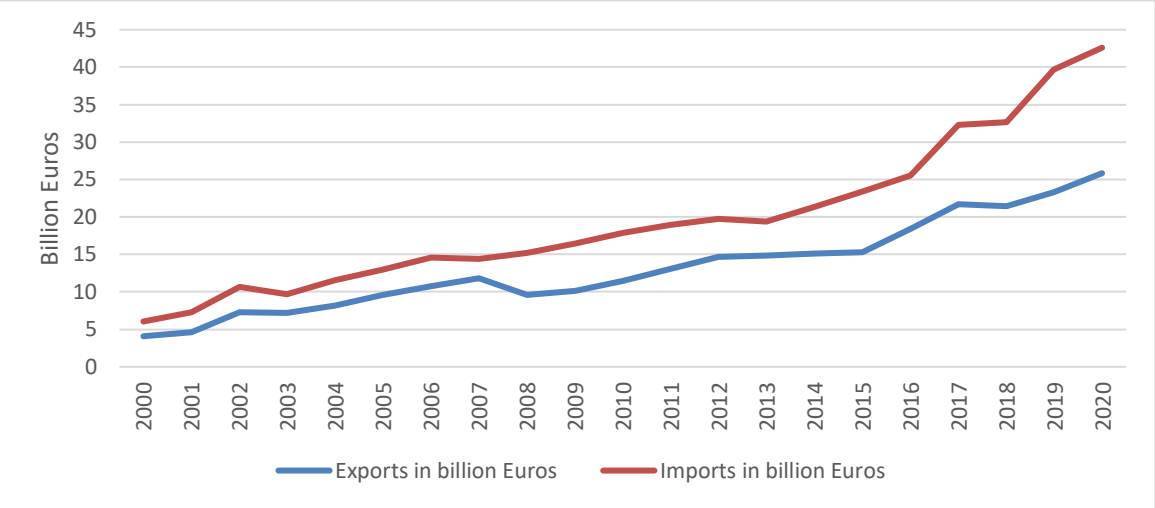


Source: Eurostat. The graph shows medicinal products exports from EU28 to Japan and Imports from Japan to EU28 countries. The definition of medicinal products includes the 126 product types listed in the Annex of the EFPIA-ECIPE report "Key Trade Data Points on the EU27 Pharmaceutical Supply Chain" published in July 2020. These 126 product types include Active Pharmaceutical Ingredients, Human Medicinal Products, Finished Pharmaceutical Products, Vaccines and Antibiotics. Values are not adjusted for inflation.

IEC-5.2: Value of medicine exports EU to Switzerland and Switzerland to EU

The next graph shows medicines exports from EU28 countries to Switzerland and Imports from Switzerland to EU28 countries. The figures show that EU exports to Switzerland displayed consistent growth across the period 2000-2020, increasing fivefold, from close to €5bn in 2000 to close to €26bn in 2020. A similar change happened with EU28 imports from Switzerland, which grew sevenfold in the same period, from €6bn in 2000 to €42bn in 2020. These patterns could reflect the positive impact of the Mutual Recognition Agreement that has been in operation since June 2002.

Figure IEC-5.2: Drug exports to and imports from Switzerland (values, bln Euro)



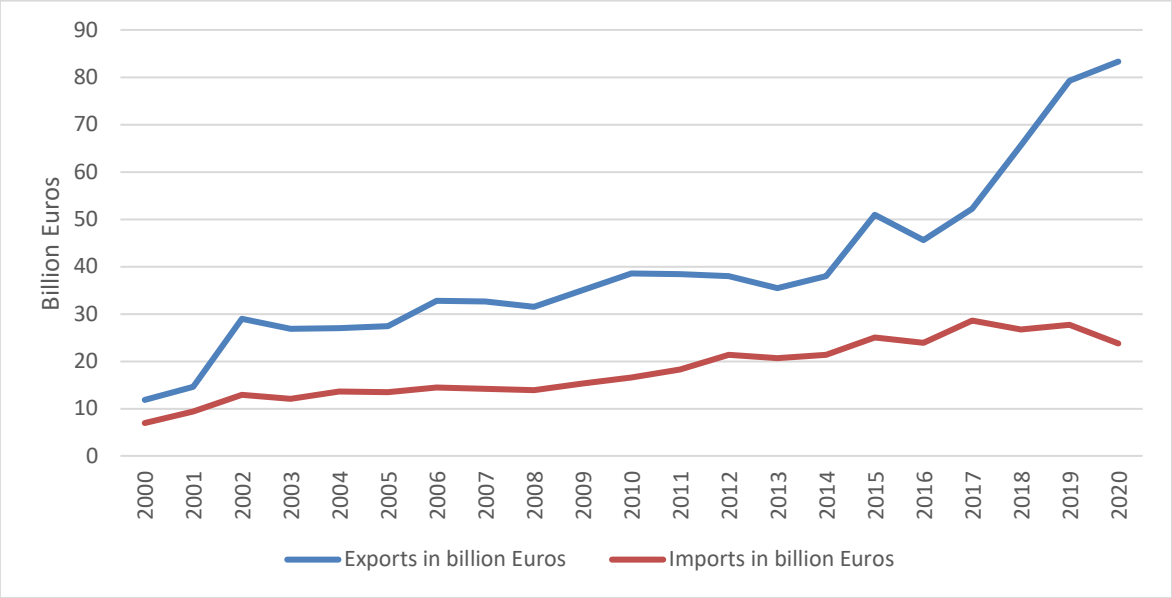
Source: Eurostat. The graph shows medicinal products exports from EU28 to Switzerland and Imports from Switzerland to EU28 countries. The definition of medicinal products includes the 126 product types listed in the Annex of the EFPIA-ECIPE report "Key Trade Data Points on the EU27 Pharmaceutical Supply Chain" published in July 2020. These 126 product types include Active Pharmaceutical Ingredients, Human Medicinal Products, Finished Pharmaceutical Products, Vaccines and Antibiotics. Values are not adjusted for inflation.

IEC-5.3: Value of medicine exports EU to USA and USA to EU

The next graph shows medicines exports from EU28 countries to the US and Imports from the US to EU28 countries.

The figures show that EU28 medicines exports to the USA displayed moderate growth during the period 2003-2010 from €27 to €38 billion Euros in 2010 and faster growth during 2017-2020 going from €52bn to €83bn. This could be triggered by the Mutual Recognition Agreement that has been in operation since November 2017. By contrast, EU28 drug imports from the USA doubled in the first 2-3 years of the new century and then took another 10 years to double again, albeit with stronger growth during the period 2008-2017 when imports grew from €14bn in 2008 to €29bn in 2017. Recent performance has shown a marked reversal, with imports falling to around €23bn.

Figure IEC-5.3: Drug exports to and imports from the US (values, bn Euro)



Source: Eurostat. The graph shows medicinal products exports from EU28 to US and Imports from US to EU28 countries. The definition of medicinal products includes the 126 product types listed in the Annex of the EFPIA-ECIPE report "Key Trade Data Points on the EU27 Pharmaceutical Supply Chain" published in July 2020. These 126 product types include Active Pharmaceutical Ingredients, Human Medicinal Products, Finished Pharmaceutical Products, Vaccines and Antibiotics. Values are not adjusted for inflation.

There is no obvious effect of the 2004 revision of the general pharmaceutical legislations in these trade data. The overall picture shows that EU trade with other key national and regional markets has grown across the 20-year period, before and after the implementation of the 2004 revisions. With exports and imports growing by 400-500% (in cash prices) across the period with each of the three trading blocs. Growth rates for both exports and imports were flatter in the 10 years or so following the introduction of the revised legislation, with growth in EU-USA trade noticeably slower in both directions during this middle-phase, before a significant strengthening of exports and slight weakening of imports in the last three years. Growth in EU-Japan trade has been more volatile, and weaker overall, but the last three years' trade figures are the inverse of the EU-US figures, with EU exports in decline and Japanese imports growing strongly.

IEC-6: Number of clinical trials performed in different geographies

Indicator definition and relevance with respect to the evaluation of IEC-6 and IEC-9

Industrial and economic competitiveness indicators 6 and 9 are related in that they measure the number of clinical trials starting in different countries of interest. As with IEC-1-4, if we consider competitiveness to mean the ability of a country or region to create welfare, taking into account the institutions, policies, and other factors that determine the level of productivity of a country or region, it is the intention of the IEC-6 and 9 indicators to measure changes in the intensity of clinical research (as a measure of productivity) in the pharmaceutical industry, both pre and post the implementation of the general pharmaceutical legislation. In order for a medicinal product to provide increased welfare in countries where it is approved, a product must successfully move through clinical research. Therefore, the aim was to observe if the EU demonstrated increased productivity following the implementation of the general pharmaceutical legislation, or if the USA, Japan, or Switzerland demonstrated increased productivity during the same period (these countries were of course assumed not to have been influenced by the implementation of the general pharmaceutical legislation). In addition, as in internal indicator for the EU, IEC-9 compares all nation states within the EU, to observe if any change in productivity was equally spread across the EU or not. In order to control for both the country of origin of the medicinal products (as defined by developer headquartered country) and for the region of approval, approvals of medicines with EU, USA, Japan, or Switzerland origin were compared in their respective home markets and the EU.

Methodology for IEC-6 and IEC-9

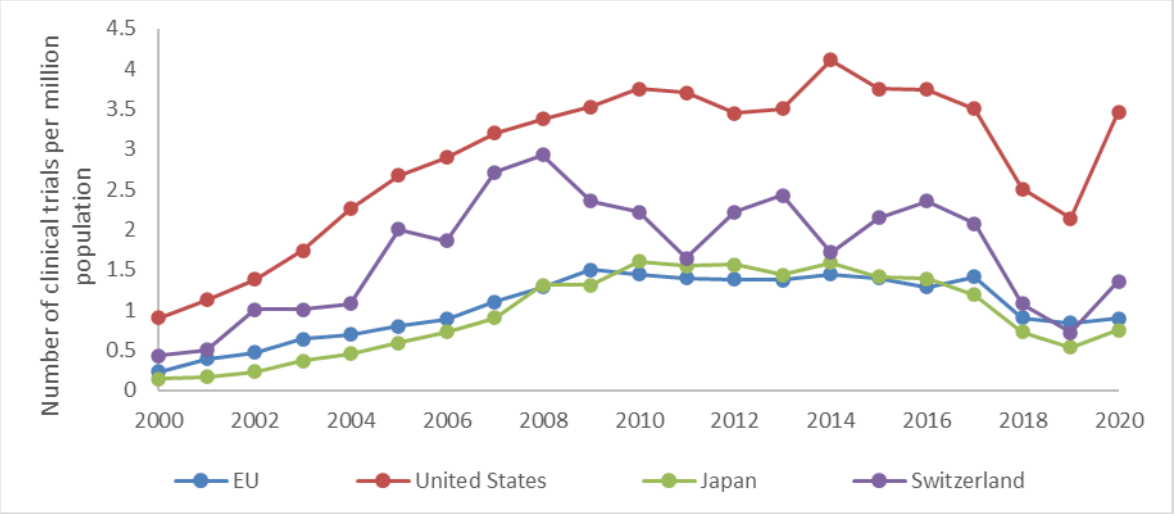
The base dataset for IEC-6 and 9 consists of over 172,000 Phase 1, Phase 2, and Phase 3 clinical trials contained in Trialtrove with start dates between 2000 and 2020. Each trial was assigned a development phase, an analysis region (USA, EU, Japan, Switzerland), and an analysis country (one of the EU28) based on the information contained in Trialtrove. In addition, only trials with known start dates and known or anticipated end dates were included. The countries in what was the EU28 were treated as always having been in the EU for the entire period of the analysis (2000-2020). Furthermore, the number of trials was adjusted based on the population of the analysis region or country in each year of the analysis period to facilitate more direct comparisons. The counts of clinical trials do not take into account the number of patients recruited in each region or country (such data are not available), so a trial with at least one site and therefore one or more patients per region or country is of necessity counted for that region or country. Trials conducted in multiple regions or countries are included as later phase trials are almost exclusively run globally or in at least two or more of the seven major pharmaceutical markets, making it impractical to exclude such trials. The mean number of clinical trials starting each year in each phase in each analysis region and country and standard deviations were determined for both the pre and post periods. As with IEC-1-4, Shapiro-Wilk tests were conducted to check data distribution prior to parametric (Welch's t-test) or non-parametric (Mann Whitney U test) tests for significance between the pre and post groups. For Phase 1 trials, Mann Whitney U tests are reported, as data were found not to fit a normal distribution. Parametric testing was preferred for Phase 2 and Phase 3, as data were found to fit a normal distribution. If the n number was lower than 30 completed trials in a phase for an analysis group, statistical analysis was not performed.

IEC-6

IEC-6 investigated the number of clinical trials starting in each year (adjusted for population) in each of the markets under investigation, namely the EU, the USA, Japan, and Switzerland, in time periods both pre and post the implementation of the 2004 revision of the general pharmaceutical legislation. Top level results comparing each analysis region for trials in Phase 1 are shown in Figure IEC6-1 and Table IEC-6.1. In

all analysis regions, the number of Phase 1 trials starting in each year was found to significantly increase in the post period compared to the pre period. Per million of population, the number of Phase 1 trials conducted in the US and Switzerland was found to be double the number in the EU or Japan.

Figure IEC6-1 Number of Phase 1 trials starting by year adjusted for population.



Source: Trialtrove 2000-2020.

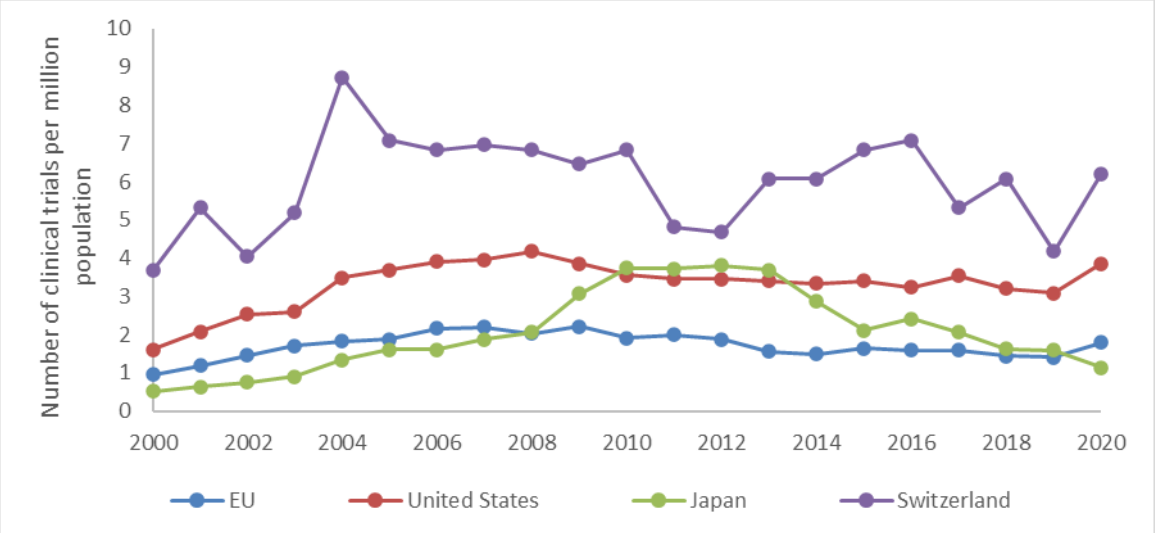
Table IEC-6.1 Descriptive statistics for the number of Phase 1 clinical trials conducted in the EU, the USA, Japan, and Switzerland

Phase	Analysis region	Pre or post	MEAN	STDEV	LOW	HIGH	N number (unadjusted number of trials)	MANN-WHITNEY U TEST (P-value)
1	EU	Pre	0.58	0.22	0.37	0.80	1,058	**0.0009**
1	EU	Post	1.27	0.22	1.05	1.50	7,756	
1	USA	Pre	1.85	0.72	1.14	2.57	2,289	**0.001**
1	USA	Post	3.42	0.51	2.91	3.94	14,758	
1	Japan	Pre	0.38	0.21	0.18	0.59	173	**0.0005**
1	Japan	Post	1.26	0.35	0.91	1.60	2,206	
1	Switzerland	Pre	1.99	1.00	0.99	2.99	56	**0.014**
1	Switzerland	Post	3.44	1.04	2.39	4.48	391	

Source: Trialtrove. Mean number of clinical trials starting each year in each phase in each analysis region and country, and standard deviations, were determined for both the pre and post periods. Shapiro-Wilk tests were conducted to check data distribution prior to non-parametric (Mann-Whitney U test) tests for significance between the pre and post groups. Significant differences between the pre and post periods are highlighted in bold.

Top level results comparing each analysis region for trials in Phase 2 are shown in Figure IEC-6.2 and Table IEC-6.2. For Japan only, the number of Phase 2 trials starting in each year was found to significantly increase in the post period compared to the pre period. No other significant differences were observed. Furthermore, there were no observable differences between the analysis regions in terms of the number of Phase 2 trials per million of population.

Figure IEC-6.2 Number of Phase 2 trials starting by year adjusted for population.



Source: Trialtrove 2000-2020.

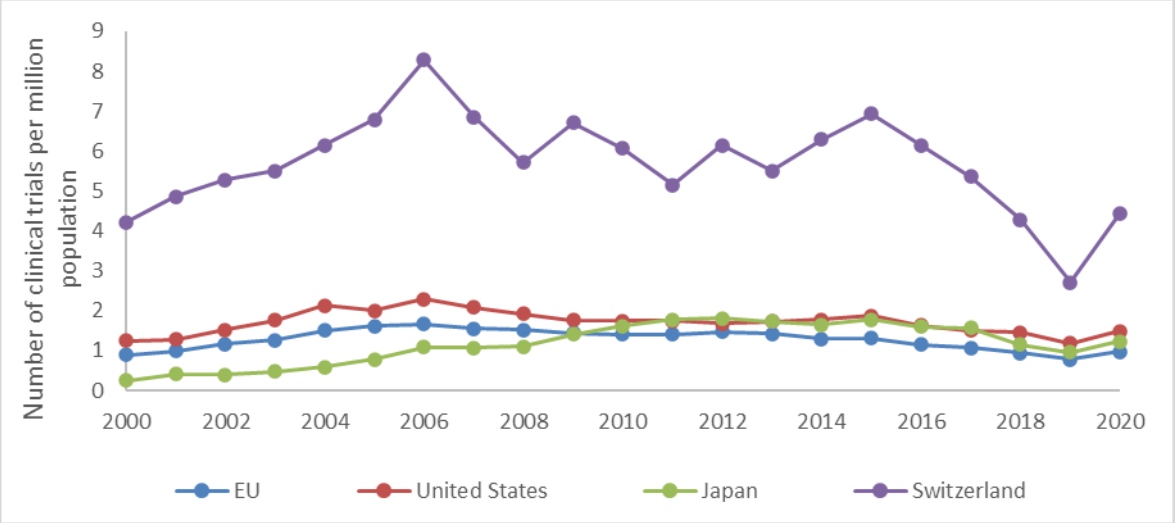
Table IEC-6.2 Descriptive statistics for the number of Phase 2 clinical trials conducted in the EU, the USA, Japan, and Switzerland

Phase	Analysis region	Pre or post	MEAN	STDEV	LOW	HIGH	N number (unadjusted number of trials)	WELCH'S T-TEST (P-value)
2	EU	Pre	1.60	0.39	1.21	1.99	3,143	0.455
2	EU	Post	1.73	0.24	1.49	1.98	10,891	
2	USA	Pre	2.84	0.80	2.04	3.65	3,803	0.093
2	USA	Post	3.51	0.29	3.22	3.80	15,315	
2	Japan	Pre	1.06	0.43	0.63	1.48	553	**0.001**
2	Japan	Post	2.61	0.90	1.71	3.51	4,579	
2	Switzerland	Pre	5.84	1.67	4.17	7.51	213	0.875
2	Switzerland	Post	5.96	0.90	5.06	6.86	667	

Source: Trialtrove. Mean number of clinical trials starting each year in each phase in each analysis region and country, and standard deviations, were determined for both the pre and post periods. Shapiro-Wilk tests were conducted to check data distribution prior to parametric (Welch's t-test) tests for significance between the pre and post groups. Significant differences between the pre and post periods are highlighted in bold.

Top level results comparing each analysis region for trials in Phase 3 are shown in Figure IEC-6.3 and Table IEC-6.3. **For Japan only, the number of Phase 3 trials starting in each year was found to significantly increase in the post period compared to the pre period. No other significant differences were observed. No difference in terms of the number of Phase 3 trials in the EU, the USA, and Japan was observed**, which is reflective of the global nature of Phase 3 development programs taking place simultaneously in the seven **major pharmaceutical markets**.

Figure IEC-6.3 Number of Phase 3 trials starting by year adjusted for population.



Source: Trialtrove 2000-2020.

Table IEC-6.3 Descriptive statistics for the number of Phase 3 clinical trials conducted in the EU, the USA, Japan, and Switzerland

Phase	Analysis region	Pre or post	MEAN	STDEV	LOW	HIGH	N number (unadjusted trials)	WELCH'S T-TEST (P-value)
3	EU	Pre	1.30	0.28	1.02	1.58	2,564	0.672
3	EU	Post	1.24	0.23	1.01	1.47	7,102	
3	USA	Pre	1.75	0.39	1.36	2.13	2,450	0.585
3	USA	Post	1.65	0.19	1.46	1.84	7,275	
3	Japan	Pre	0.56	0.26	0.30	0.82	269	**0.002**
3	Japan	Post	1.49	0.28	1.21	1.76	2,609	
3	Switzerland	Pre	5.87	1.25	4.61	7.12	364	0.549
3	Switzerland	Post	5.49	1.10	4.39	6.60	996	

Source: Trialtrove. Mean number of clinical trials starting each year in each phase in each analysis region and country, and standard deviations, were determined for both the pre and post periods. Shapiro-Wilk tests were conducted to check data distribution prior to parametric (Welch's t-test) tests for significance between the pre and post groups. Significant differences between the pre and post periods are highlighted in bold.

Table IEC-6.4 shows the splits by therapy area for each region for total trials, ignoring phase. Broadly similar trends in terms of the therapy areas with significant differences were observed between analysis regions, with numbers of trials for Autoimmune, CNS, Infectious disease, Metabolic, and Oncology all seeing significant differences between the pre and post periods.

Table IEC-6.4 Descriptive statistics for the number of clinical trials conducted in the EU, the USA, Japan, and Switzerland, split by therapy area

Therapy area	Analysis region	Pre or post	MEAN	STDEV	LOW	HIGH	N number (unadjusted trials)	WELCH'S T-TEST (P-value)
Autoimmune	EU	Pre	0.71	0.18	0.53	0.89	1,440	**0.009**
Autoimmune	EU	Post	1.07	0.12	0.95	1.20	6,622	
Autoimmune	USA	Pre	0.83	0.23	0.59	1.06	1,185	**0.003**
Autoimmune	USA	Post	1.33	0.12	1.21	1.46	5,759	
Autoimmune	Japan	Pre	0.31	0.15	0.16	0.47	174	**0.001**
Autoimmune	Japan	Post	1.14	0.24	0.90	1.37	1,969	
Autoimmune	Switzerland	Pre	1.83	0.71	1.13	2.54	115	0.579
Autoimmune	Switzerland	Post	2.03	0.34	1.69	2.38	397	
Cardiovascular	EU	Pre	0.49	0.18	0.32	0.67	955	0.089
Cardiovascular	EU	Post	0.71	0.15	0.56	0.86	4407	
Cardiovascular	USA	Pre	0.63	0.22	0.41	0.84	878	0.089
Cardiovascular	USA	Post	0.83	0.14	0.69	0.97	3648	
Cardiovascular	Japan	Pre	0.38	0.18	0.20	0.56	201	0.001
Cardiovascular	Japan	Post	1.05	0.36	0.69	1.41	1865	
Cardiovascular	Switzerland	Pre	1.61	0.55	1.06	2.16	102	0.144
Cardiovascular	Switzerland	Post	2.01	0.43	1.58	2.44	392	
CNS	EU	Pre	0.60	0.21	0.38	0.07	1162	**0.015**
CNS	EU	Post	0.97	0.18	0.78	0.16	6036	
CNS	USA	Pre	1.35	0.51	0.84	0.14	1906	**0.021**
CNS	USA	Post	2.10	0.09	2.00	0.31	9081	
CNS	Japan	Pre	0.19	0.08	0.11	0.06	104	**0.001**
CNS	Japan	Post	0.81	0.16	0.66	0.31	1422	
CNS	Switzerland	Pre	1.42	0.74	0.68	0.35	91	**0.022**
CNS	Switzerland	Post	2.08	0.44	1.64	0.49	409	
Genitourinary	EU	Pre	0.14	0.06	0.09	0.20	289	0.385
Genitourinary	EU	Post	0.18	0.04	0.13	0.22	1,096	
Genitourinary	USA	Pre	0.14	0.06	0.08	0.19	191	0.073
Genitourinary	USA	Post	0.20	0.05	0.15	0.25	867	
Genitourinary	Japan	Pre	0.05	0.02	0.03	0.07	30	Not determined
Genitourinary	Japan	Post	0.14	0.06	0.08	0.20	244	
Genitourinary	Switzerland	Pre	0.19	0.15	0.04	0.34	12	Not determined
Genitourinary	Switzerland	Post	0.20	0.12	0.08	0.32	42	
Infectious disease	EU	Pre	0.50	0.11	0.39	0.61	1011	**0.005**

Infectious disease	EU	Post	0.79	0.20	0.59	0.98	4,866	
Infectious disease	USA	Pre	0.69	0.21	0.48	0.90	967	**0.001**
Infectious disease	USA	Post	1.25	0.26	0.99	1.52	5,381	
Infectious disease	Japan	Pre	0.17	0.12	0.05	0.28	78	**0.001**
Infectious disease	Japan	Post	0.61	0.18	0.43	0.80	1,074	
Infectious disease	Switzerland	Pre	1.24	0.21	1.03	1.45	84	0.156
Infectious disease	Switzerland	Post	1.46	0.40	1.05	1.86	294	
Metabolic	EU	Pre	0.43	0.14	0.28	0.57	851	**0.035**
Metabolic	EU	Post	0.70	0.11	0.58	0.81	4,314	
Metabolic	USA	Pre	0.74	0.26	0.48	1.00	1,055	**0.017**
Metabolic	USA	Post	1.13	0.18	0.96	1.31	4,962	
Metabolic	Japan	Pre	0.27	0.18	0.09	0.44	130	**0.001**
Metabolic	Japan	Post	1.40	0.51	0.89	1.91	2,430	
Metabolic	Switzerland	Pre	1.32	0.61	0.71	1.93	82	0.781
Metabolic	Switzerland	Post	1.24	0.46	0.78	1.69	251	
Oncology	EU	Pre	1.32	0.25	1.07	1.57	2,808	0.408
Oncology	EU	Post	1.50	0.27	1.23	1.77	9,322	
Oncology	USA	Pre	2.70	0.61	2.10	3.31	3,888	**0.032**
Oncology	USA	Post	3.51	0.57	2.94	4.08	15,290	
Oncology	Japan	Pre	0.94	0.33	0.61	1.27	534	**0.001**
Oncology	Japan	Post	2.87	1.07	1.79	3.94	5,013	
Oncology	Switzerland	Pre	4.17	0.95	3.22	5.12	281	0.713
Oncology	Switzerland	Post	4.37	1.13	3.24	5.51	871	
Ophthalmology	EU	Pre	0.05	0.03	0.02	0.07	84	**0.006**
Ophthalmology	EU	Post	0.13	0.03	0.10	0.16	781	
Ophthalmology	USA	Pre	0.09	0.05	0.03	0.14	108	**0.001**
Ophthalmology	USA	Post	0.26	0.05	0.21	0.31	1127	
Ophthalmology	Japan	Pre	0.03	0.02	0.01	0.06	18	Not determined
Ophthalmology	Japan	Post	0.22	0.08	0.14	0.31	386	
Ophthalmology	Switzerland	Pre	0.17	0.19	-0.02	0.35	7	Not determined
Ophthalmology	Switzerland	Post	0.34	0.15	0.18	0.49	65	
Vaccines	EU	Pre	0.12	0.05	0.07	0.17	226	0.328
Vaccines	EU	Post	0.18	0.07	0.10	0.25	1140	
Vaccines	USA	Pre	0.17	0.09	0.08	0.26	214	**0.016**
Vaccines	USA	Post	0.31	0.06	0.25	0.36	1341	
Vaccines	Japan	Pre	0.02	0.02	0.00	0.04	5	Not determined
Vaccines	Japan	Post	0.13	0.05	0.08	0.18	229	

Vaccines	Switzerland	Pre	0.20	0.13	0.07	0.33	11	Not determined
Vaccines	Switzerland	Post	0.71	0.18	0.53	0.89	1,440	

Source: Trialtrove. Mean number of clinical trials starting each year in each phase in each analysis region and country, and standard deviations, were determined for both the pre and post periods. Shapiro-Wilk tests were conducted to check data distribution prior to parametric (Welch's t-test) tests for significance between the pre and post groups. Significant differences between the pre and post periods are highlighted in bold.

Interpretation of possible causes for changes in IEC-6

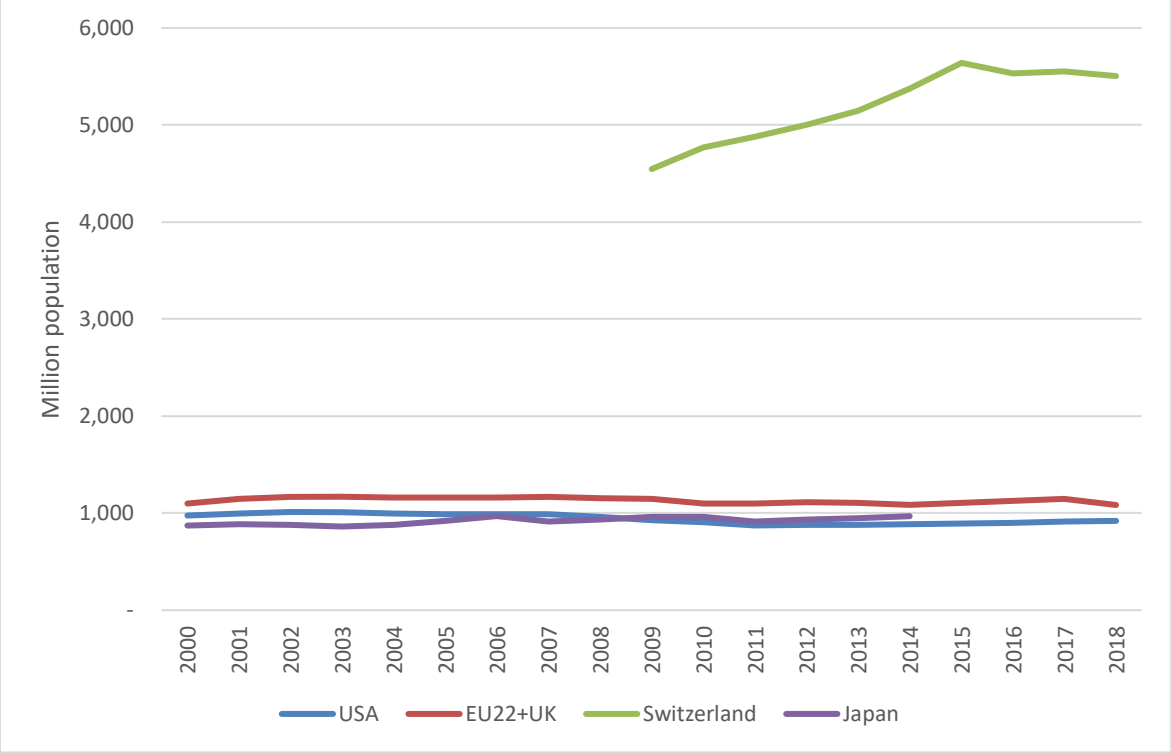
Regarding Phase 1 trials, all analysis regions were shown to increase in productivity (number of Phase 1 clinical trials starting each year), so it is unclear if the implementation of the general pharmaceutical legislation had an impact on increasing the productivity in the EU with regards to Phase 1 trials. At Phase 2 and Phase 3, only Japan saw an increase in productivity (number of trials starting in each year). This is possibly a function of the reduction in the "drug lag" between Japan and the other major pharmaceutical markets in the USA and Europe in terms of drug development over the last 20 years, but may also be an artefact of increasing data availability from Japan, which has also improved over the last 20 years.

IEC-7: Employment in the pharmaceutical industry

Statistics show that employment has grown only very slightly across the 20-year period under review, notwithstanding the stronger growth in trade and productivity figures. There is no evident major change in overall employment in the years following the implementation of the 2004 revision of the legislation, and the EU trend, such as it is, mirrors that of the industry in the USA.

The total number of employees in the pharmaceutical industry across the 22 EU countries that report this information in the OECD STAN database plus UK has remained stable over the period 2000-2020, averaging 1131 employees per million population. Something similar occurs with the US over this period and with Japan during 2000 - 2014, both countries with a close average of 942 and 921 employees per million population, respectively. In Switzerland, on the other hand, there has been a significant growth in this indicator during the period 2009-2015, from 4546 to 5640 employees per million population, followed by a slowdown in 2016-2018.

Figure IEC-7: Number of employees in the pharmaceutical sector per million population

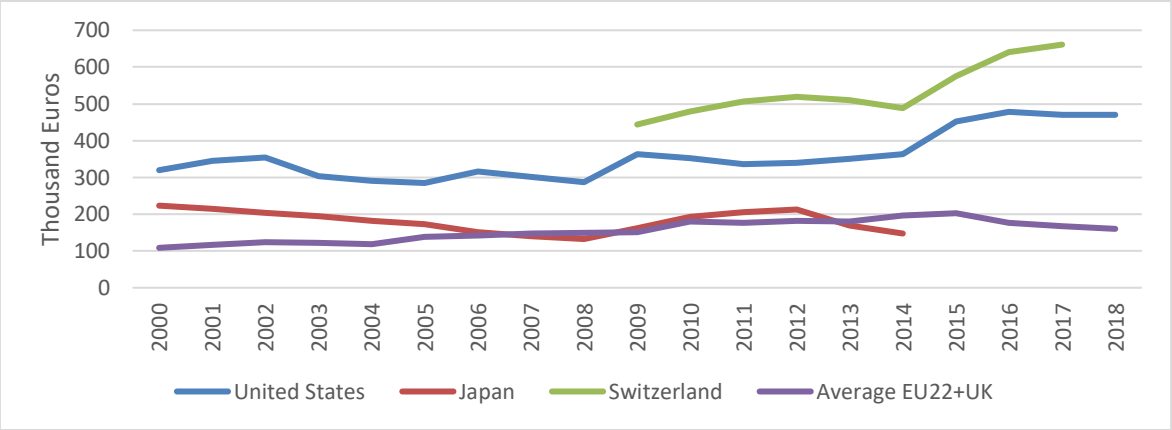


Source: OECD STAN database. The figure shows the number of employees in the pharmaceutical sector per million population in USA, Switzerland, Japan and the UK+ EU22 countries including: Austria, Belgium, Czech, Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Netherlands, Poland, Portugal, Slovak Republic, Slovenia, Spain and Sweden.

IEC-8: GVA contribution of the pharmaceutical industry

The gross value added per employee (GVA/employee) in Europe displayed significant growth in the 5-year period 2005-2010, when it reached €181k per employee, followed by a slight decline in 2011-2013 and another period of growth during 2014-2015 and a slowdown in 2017-2018. In 2018, EU GVA/employee stood at €160k per employee. The US data mirror the trend in the EU figures although in general US workers productivity is on average 2.3 times higher during the complete period. Furthermore, since 2015 there is consistent growth in labour productivity which stands at €364k per employee in 2018. On this analysis, there has been no obvious loss or improvement in Europe's competitiveness vis a vis the pharmaceutical industry in the USA close to the time when the EU General Pharmaceutical legislation came into force in 2004-2005.

Figure IEC-8: Gross value added per employee in the pharmaceutical sector

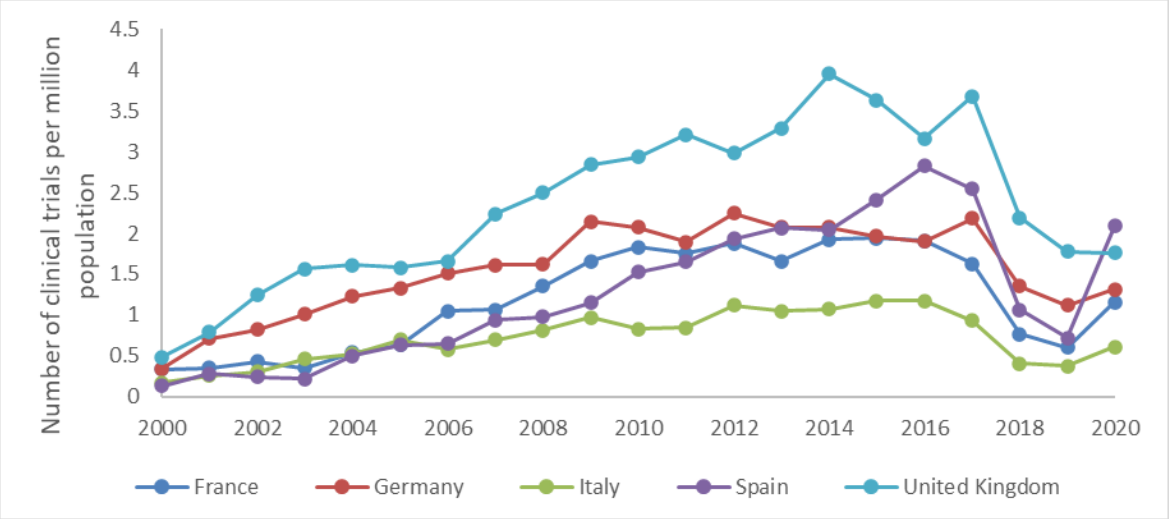


Source: OECD STAN database for indicators of value added in thousand euros and total employment in the pharmaceutical sector. GVA per employee was computed dividing GVA by the number of employees. The average for EU22 + UK is unweighted. Figures are not adjusted for inflation.

IEC-9: Number of clinical trials conducted in the European countries

IEC-9 investigated the number of clinical trials starting in each year in each phase of development in each of the EU28 countries in time periods both pre and post the implementation of the 2004 revision of the general pharmaceutical legislation. Top level results comparing the EU28 countries for trials in Phase 1 are shown in Table IEC-9.1, and illustrative data for the top 5 pharma markets in the EU are shown in Figure IEC-9.1. In all countries shown, the number of Phase 1 trials adjusted for population starting in each year was found to significantly increase in the post period compared to the pre period. Differences in trials at all phases by therapy area were also investigated. However, outside of the 5 major markets, n numbers found are too low to infer any significant differences, thus data for France, Germany, Italy, Spain, and the UK only are presented.

Figure IEC-9.1 Number of Phase 1 trials starting by year for top 5 largest pharma markets in the EU adjusted for population.



Source: Trialtrove 2000-2020.

Table IEC-9.1 Descriptive statistics for the number of Phase 1 clinical trials adjusted for population conducted in the EU28 countries

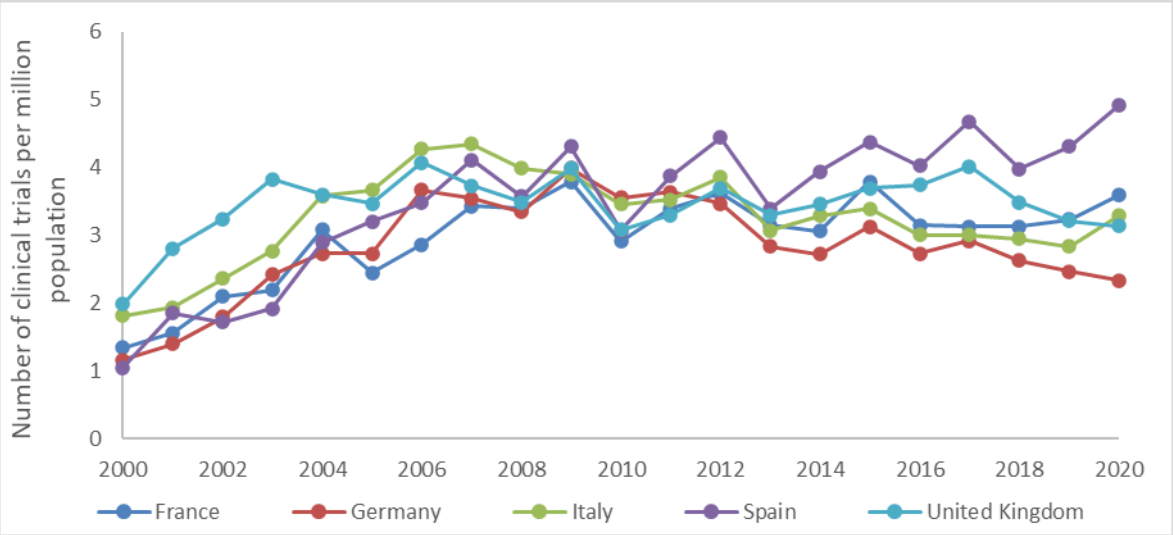
Phase	Analysis region	Pre or post	MEAN	STDEV	LOW	HIGH	N number (unadjusted trials)	MANN-WHITNEY U TEST (P-value)
1	France	Pre	0.53	0.23	0.29	0.76	131	**0.0004**
1	France	Post	1.54	0.43	1.11	1.97	1,373	
1	Germany	Pre	0.99	0.37	0.62	1.37	337	**0.001**
1	Germany	Post	1.84	0.35	1.49	2.20	2,097	
1	Italy	Pre	0.43	0.18	0.25	0.60	101	**0.0003**
1	Italy	Post	0.87	0.26	0.62	1.13	711	
1	Spain	Pre	0.38	0.20	0.18	0.58	63	**0.0004**
1	Spain	Post	1.77	0.63	1.14	2.40	1101	
1	United Kingdom	Pre	1.28	0.43	0.85	1.71	353	**0.0007**
1	United Kingdom	Post	2.92	0.67	2.25	3.58	2489	
1	Poland	Pre	0.15	0.11	0.04	0.26	20	Not determined
1	Poland	Post	0.59	0.15	0.43	0.74	314	
1	Romania	Pre	0.04	0.04	0.00	0.08	3	Not determined
1	Romania	Post	0.34	0.15	0.18	0.49	89	
1	Netherlands	Pre	1.73	0.78	0.95	2.51	119	**0.0006**
1	Netherlands	Post	5.01	0.97	4.04	5.99	1176	
1	Greece	Pre	0.23	0.12	0.12	0.35	12	Not determined
1	Greece	Post	0.54	0.22	0.32	0.76	81	
1	Czech Republic	Pre	0.31	0.28	0.03	0.59	14	Not determined
1	Czech Republic	Post	1.50	0.57	0.93	2.07	202	
1	Austria	Pre	0.86	0.48	0.37	1.34	25	Not determined
1	Austria	Post	2.25	0.65	1.60	2.90	250	
1	Belgium	Pre	2.03	0.98	1.04	3.01	84	**0.001**
1	Belgium	Post	6.78	1.48	5.30	8.25	1032	
1	Bulgaria	Pre	0.08	0.07	0.01	0.15	2	Not determined
1	Bulgaria	Post	1.29	0.52	0.77	1.81	120	
1	Croatia	Pre	0.21	0.16	0.05	0.37	3	Not determined
1	Croatia	Post	0.35	0.36	-0.01	0.71	19	
1	Cyprus	Pre	0.00	0.00	0.00	0.00	0	Not determined
1	Cyprus	Post	0.23	0.42	-0.19	0.65	3	
1	Denmark	Pre	1.67	1.16	0.51	2.82	30	Not determined
1	Denmark	Post	3.90	1.47	2.43	5.37	326	
1	Estonia	Pre	0.14	0.35	-0.21	0.49	1	Not determined
1	Estonia	Post	1.46	1.28	0.18	2.74	20	
1	Finland	Pre	0.63	0.47	0.16	1.10	11	Not determined
1	Finland	Post	1.83	0.64	1.19	2.47	122	
1	Hungary	Pre	0.23	0.17	0.05	0.40	7	Not determined
1	Hungary	Post	1.47	0.49	0.98	1.96	203	
1	Ireland	Pre	0.26	0.18	0.08	0.43	4	

1	Ireland	Post	1.05	0.56	0.49	1.61	76	Not determined
1	Latvia	Pre	0.00	0.00	0.00	0.00	0	Not determined
1	Latvia	Post	0.96	0.75	0.22	1.71	25	
1	Lithuania	Pre	0.05	0.12	-0.07	0.16	1	Not determined
1	Lithuania	Post	0.56	0.55	0.02	1.11	22	
1	Luxembourg	Pre	0.29	0.70	-0.41	0.99	1	Not determined
1	Luxembourg	Post	0.31	0.72	-0.41	1.03	2	
1	Malta	Pre	0.00	0.00	0.00	0.00	0	Not determined
1	Malta	Post	0.00	0.00	0.00	0.00	0	
1	Portugal	Pre	0.30	0.17	0.13	0.47	12	Not determined
1	Portugal	Post	0.29	0.17	0.12	0.47	47	
1	Slovakia	Pre	0.26	0.23	0.03	0.49	3	Not determined
1	Slovakia	Post	0.88	0.40	0.47	1.28	63	
1	Slovenia	Pre	0.14	0.23	-0.08	0.37	2	Not determined
1	Slovenia	Post	0.81	0.50	0.31	1.31	22	
1	Sweden	Pre	1.13	0.78	0.35	1.90	32	0.002
1	Sweden	Post	2.95	1.27	1.68	4.22	382	

Source: Trialtrove and Pharmaprojects. Mean number of clinical trials starting each year in each phase in each analysis region and country, and standard deviations, were determined for both the pre and post periods. Shapiro-Wilk tests were conducted to check data distribution prior to non-parametric (Mann-Whitney U test) tests for significance between the pre and post groups. Significant differences between the pre and post periods are highlighted in bold.

Top level results comparing the EU28 countries for trials in Phase 2 are shown in Table IEC-9.2and illustrative data for the top 5 pharma markets in the EU28 are shown in Figure IEC-9.2. For France, Spain, Poland, Romania, Greece, and the Czech Republic, the number of Phase 2 trials starting in each year was found to significantly increase in the post period compared to the pre period.

Figure IEC-9.2 Number of Phase 2 trials starting by year for top 5 largest pharma markets in the EU.



Source: Trialtrove 2000-2020.

Table IEC-9.2 Descriptive statistics for the number of Phase 2 clinical trials conducted in the EU28 countries

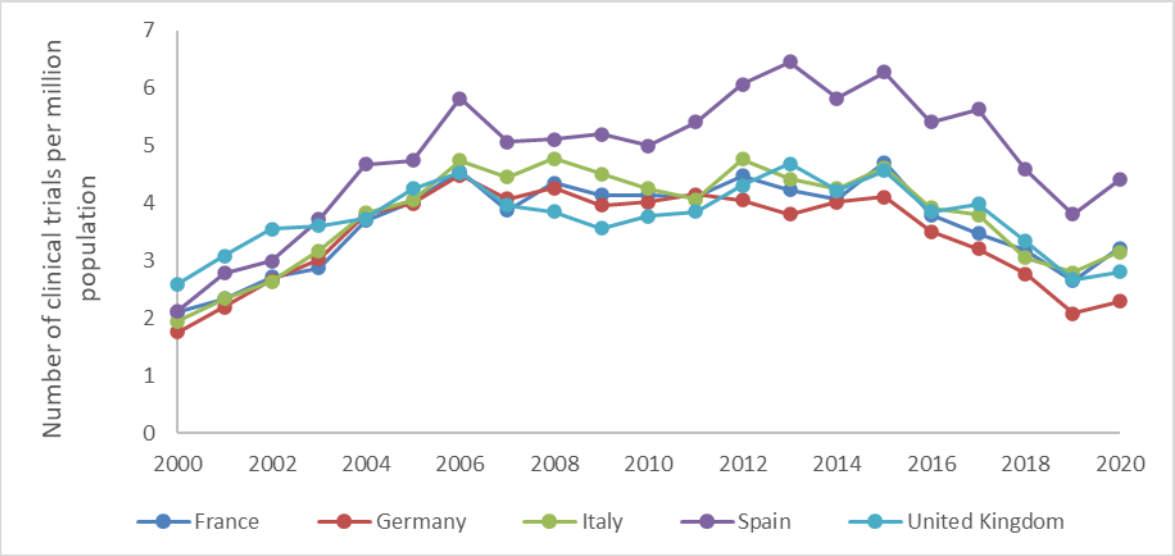
Phase	Analysis region	Pre or post	MEAN	STDEV	LOW	HIGH	N number (unadjusted trials)	WELCH'S T-TEST (P-value)
2	France	Pre	2.22	0.59	1.63	2.81	893	**0.003**
2	France	Post	3.33	0.28	3.05	3.60	3,538	
2	Germany	Pre	2.27	0.81	1.46	3.08	1,101	0.06
2	Germany	Post	3.05	0.48	2.57	3.54	4,128	
2	Italy	Pre	2.91	0.87	2.04	3.78	822	0.273
2	Italy	Post	3.35	0.37	2.98	3.72	3,354	
2	Spain	Pre	2.30	0.83	1.47	3.13	750	**0.001**
2	Spain	Post	4.06	0.50	3.57	4.56	3,416	
2	United Kingdom	Pre	3.28	0.65	2.63	3.93	1,027	0.454
2	United Kingdom	Post	3.50	0.29	3.21	3.80	3,315	
2	Poland	Pre	1.42	0.71	0.71	2.12	540	**0.0002**
2	Poland	Post	3.19	0.51	2.68	3.71	3,004	
2	Romania	Pre	1.10	0.74	0.36	1.84	165	**0.005**
2	Romania	Post	2.35	0.69	1.65	3.04	1,583	
2	Netherlands	Pre	5.24	1.70	3.54	6.93	615	0.051
2	Netherlands	Post	6.93	0.79	6.14	7.72	2,083	
2	Greece	Pre	1.87	0.65	1.22	2.52	231	**0.003**
2	Greece	Post	3.08	0.61	2.47	3.70	1,027	
2	Czech Republic	Pre	3.61	2.51	1.10	6.13	375	**0.004**
2	Czech Republic	Post	8.08	1.06	7.02	9.13	2,188	
2	Austria	Pre	11.09	4.87	6.22	15.96	379	**0.045**
2	Austria	Post	14.04	2.96	11.08	17.00	1,611	

2	Belgium	Pre	11.88	4.77	7.12	16.65	570	**0.013**
2	Belgium	Post	15.69	2.81	12.88	18.50	2,400	
2	Bulgaria	Pre	4.39	3.08	1.31	7.46	105	**0.001**
2	Bulgaria	Post	13.85	2.87	10.98	16.71	1,313	
2	Croatia	Pre	5.71	3.13	2.58	8.85	86	0.041
2	Croatia	Post	10.44	2.93	7.51	13.37	583	
2	Cyprus	Pre	5.86	11.92	-6.06	17.78	38	Not determined
2	Cyprus	Post	1.46	1.01	0.45	2.47	22	
2	Denmark	Pre	13.26	4.96	8.30	18.22	329	**0.003**
2	Denmark	Post	16.19	2.87	13.32	19.06	1,367	
2	Estonia	Pre	30.71	16.10	14.61	46.82	118	**0.015**
2	Estonia	Post	45.46	10.30	35.16	55.76	641	
2	Finland	Pre	15.74	4.59	11.16	20.33	343	**0.777**
2	Finland	Post	13.72	3.90	9.83	17.62	982	
2	Hungary	Pre	8.94	3.59	5.36	12.53	360	**0.001**
2	Hungary	Post	15.95	3.12	12.83	19.08	2,219	
2	Ireland	Pre	7.11	1.87	5.24	8.98	153	**0.005**
2	Ireland	Post	9.51	2.42	7.09	11.93	666	
2	Latvia	Pre	11.64	7.00	4.64	18.65	85	**0.005**
2	Latvia	Post	22.31	4.94	17.36	27.25	620	
2	Lithuania	Pre	10.86	6.83	4.03	17.68	112	**0.017**
2	Lithuania	Post	17.03	4.95	12.08	21.97	724	
2	Luxembourg	Pre	4.00	2.83	1.17	6.83	11	0.591
2	Luxembourg	Post	5.38	2.76	2.62	8.15	37	
2	Malta	Pre	1.71	2.71	-1.00	4.42	1	Not determined
2	Malta	Post	1.69	3.22	-1.53	4.91	14	
2	Portugal	Pre	5.47	1.86	3.61	7.33	229	0.080
2	Portugal	Post	6.82	1.24	5.58	8.05	948	
2	Slovakia	Pre	8.91	4.23	4.69	13.14	168	0.060
2	Slovakia	Post	14.98	4.45	10.53	19.44	1054	
2	Slovenia	Pre	6.21	1.56	4.66	7.77	55	**0.001**
2	Slovenia	Post	7.92	2.62	5.31	10.54	221	
2	Sweden	Pre	11.35	3.29	8.06	14.64	460	**0.005**
2	Sweden	Post	11.95	3.41	8.54	15.35	1531	

Source: Trialtrove and Pharmaprojects. Mean number of clinical trials starting each year in each phase in each analysis region and country, and standard deviations, were determined for both the pre and post periods. Shapiro-Wilk tests were conducted to check data distribution prior to parametric (Welch's t-test) tests for significance between the pre and post groups. Significant differences between the pre and post periods are highlighted in bold.

Top level results comparing the EU28 countries by population for trials in Phase 3 are shown in Table IEC-9.3 and illustrative data for the top 5 pharma markets in the EU are shown in Figure IEC-9.3. For Spain, Poland, Romania, Greece, and the Czech Republic, the number of Phase 3 trials starting in each year was found to significantly increase in the post period compared to the pre period.

Figure IEC-9.3 Number of Phase 3 trials starting by year for top 5 largest pharma markets in the EU.



Source: Trialtrove 2000-2020.

Table IEC-9.3 Descriptive statistics for the number of Phase 3 clinical trials conducted in the EU28 countries

Phase	Analysis region	Pre or post	MEAN	STDEV	LOW	HIGH	N number (unadjusted trials)	WELCH'S T-TEST (P-value)
3	France	Pre	3.19	0.85	2.34	4.03	893	0.1
3	France	Post	3.89	0.57	3.32	4.46	3,538	
3	Germany	Pre	3.13	0.93	2.20	4.06	1,101	0.345
3	Germany	Post	3.56	0.71	2.85	4.27	4,128	
3	Italy	Pre	3.25	0.93	2.31	4.18	822	0.098
3	Italy	Post	4.03	0.64	3.39	4.67	3,354	
3	Spain	Pre	3.84	1.21	2.63	5.05	750	**0.024**
3	Spain	Post	5.32	0.58	4.74	5.90	3,416	
3	United Kingdom	Pre	3.62	0.61	3.01	4.23	1,027	0.548
3	United Kingdom	Post	3.81	0.58	3.23	4.39	3,315	
3	Poland	Pre	3.48	1.30	2.18	4.77	540	**0.005**
3	Poland	Post	5.67	0.92	4.75	6.59	3,004	
3	Romania	Pre	2.36	1.44	0.92	3.80	165	**0.001**
3	Romania	Post	5.69	1.82	3.87	7.51	1,583	
3	Netherlands	Pre	8.13	1.75	6.38	9.87	615	0.492
3	Netherlands	Post	8.73	1.59	7.14	10.32	2,083	
3	Greece	Pre	4.82	1.39	3.43	6.20	231	**0.019**
3	Greece	Post	6.66	1.26	5.40	7.92	1,027	
3	Czech Republic	Pre	9.63	4.19	5.44	13.82	375	**0.012**
3	Czech Republic	Post	15.64	2.84	12.80	18.48	2,188	
3	Austria	Pre	11.09	4.87	6.22	15.96	379	0.213

3	Austria	Post	14.04	2.96	11.08	17.00	1,611	
3	Belgium	Pre	11.88	4.77	7.12	16.65	570	0.051
3	Belgium	Post	15.69	2.81	12.88	18.50	2,400	
3	Bulgaria	Pre	4.39	3.08	1.31	7.46	105	**0.001**
3	Bulgaria	Post	13.85	2.87	10.98	16.71	1,313	
3	Croatia	Pre	5.71	3.13	2.58	8.85	86	**0.005**
3	Croatia	Post	10.44	2.93	7.51	13.37	583	
3	Cyprus	Pre	5.86	11.92	-6.06	17.78	38	0.737
3	Cyprus	Post	1.46	1.01	0.45	2.47	22	
3	Denmark	Pre	13.26	4.96	8.30	18.22	329	0.219
3	Denmark	Post	16.19	2.87	13.32	19.06	1,367	
3	Estonia	Pre	30.71	16.10	14.61	46.82	118	0.071
3	Estonia	Post	45.46	10.30	35.16	55.76	641	
3	Finland	Pre	15.74	4.59	11.16	20.33	343	0.591
3	Finland	Post	13.72	3.90	9.83	17.62	982	
3	Hungary	Pre	8.94	3.59	5.36	12.53	360	**0.002**
3	Hungary	Post	15.95	3.12	12.83	19.08	2,219	
3	Ireland	Pre	7.11	1.87	5.24	8.98	153	**0.035**
3	Ireland	Post	9.51	2.42	7.09	11.93	666	
3	Latvia	Pre	11.64	7.00	4.64	18.65	85	**0.009**
3	Latvia	Post	22.31	4.94	17.36	27.25	620	
3	Lithuania	Pre	10.86	6.83	4.03	17.68	112	0.080
3	Lithuania	Post	17.03	4.95	12.08	21.97	724	
3	Luxembourg	Pre	4.00	2.83	1.17	6.83	11	Not determined
3	Luxembourg	Post	5.38	2.76	2.62	8.15	37	
3	Malta	Pre	1.71	2.71	-1.00	4.42	1	Not determined
3	Malta	Post	1.69	3.22	-1.53	4.91	14	
3	Portugal	Pre	5.47	1.86	3.61	7.33	229	0.144
3	Portugal	Post	6.82	1.24	5.58	8.05	948	
3	Slovakia	Pre	8.91	4.23	4.69	13.14	168	**0.015**
3	Slovakia	Post	14.98	4.45	10.53	19.44	1,054	
3	Slovenia	Pre	6.21	1.56	4.66	7.77	55	0.101
3	Slovenia	Post	7.92	2.62	5.31	10.54	221	
3	Sweden	Pre	11.35	3.29	8.06	14.64	460	0.725
3	Sweden	Post	11.95	3.41	8.54	15.35	1,531	

Source: Trialtrove and Pharmaprojects. Mean number of clinical trials starting each year in each phase in each analysis region and country, and standard deviations, were determined for both the pre and post periods. Shapiro-Wilk tests were conducted to check data distribution prior to parametric (Welch's t-test) tests for significance between the pre and post groups. Significant differences between the pre and post periods are highlighted in bold.

Table IEC-9.4 shows splits by therapy area for each region for total trials adjusted for population, ignoring phase, in the top 5 largest pharmaceutical markets in the EU. In terms of trends, only trials for Autoimmune diseases significantly increased in all countries in the post period compared to the pre period. Cardiovascular trials significantly increased in Spain and the UK, CNS trials in France, Italy, and Spain, Infectious disease trials in France, Spain, and the UK, and Oncology trials in France, Spain, and the UK. N numbers were not sufficient in any country to perform statistical tests for Ophthalmology or Vaccines.

Table IEC-9.4 Descriptive statistics for the number of clinical trials conducted in France, Germany, Italy, Spain, and the UK, split by therapy area

Therapy area	Analysis country	Pre or post	MEAN	STDEV	LOW	HIGH	N number (unadjusted trials)	WELCH'S T-TEST (P-value)
Autoimmune	France	Pre	1.13	0.30	0.83	1.42	320	**0.002**
Autoimmune	France	Post	1.72	0.22	1.50	1.93	1551	
Autoimmune	Germany	Pre	1.40	0.49	0.90	1.89	467	**0.005**
Autoimmune	Germany	Post	2.23	0.32	1.91	2.55	2571	
Autoimmune	Italy	Pre	1.10	0.38	0.72	1.48	267	**0.016**
Autoimmune	Italy	Post	1.62	0.24	1.38	1.86	1349	
Autoimmune	Spain	Pre	1.20	0.41	0.78	1.61	225	**0.001**
Autoimmune	Spain	Post	2.26	0.37	1.89	2.63	1441	
Autoimmune	United Kingdom	Pre	1.96	0.38	1.58	2.33	561	**0.008**
Autoimmune	United Kingdom	Post	2.56	0.39	2.17	2.95	2197	
Cardiovascular	France	Pre	0.88	0.26	0.62	1.14	251	0.123
Cardiovascular	France	Post	1.08	0.20	0.88	1.29	991	
Cardiovascular	Germany	Pre	1.12	0.39	0.72	1.51	368	0.793
Cardiovascular	Germany	Post	1.18	0.34	0.85	1.52	1379	
Cardiovascular	Italy	Pre	1.14	0.36	0.78	1.50	290	0.265
Cardiovascular	Italy	Post	1.34	0.34	1.00	1.69	1124	
Cardiovascular	Spain	Pre	1.08	0.37	0.71	1.46	203	**0.038**
Cardiovascular	Spain	Post	1.49	0.23	1.26	1.73	952	
Cardiovascular	United Kingdom	Pre	1.13	0.34	0.78	1.47	302	0.086
Cardiovascular	United Kingdom	Post	1.44	0.28	1.16	1.71	1252	
CNS	France	Pre	0.99	0.44	0.55	1.43	254	**0.017**
CNS	France	Post	1.58	0.26	1.32	1.84	1450	
CNS	Germany	Pre	1.17	0.51	0.66	1.68	383	0.254
CNS	Germany	Post	1.45	0.41	1.05	1.86	1717	
CNS	Italy	Pre	0.93	0.48	0.45	1.42	200	**0.086**
CNS	Italy	Post	1.34	0.15	1.20	1.49	1140	
CNS	Spain	Pre	1.19	0.50	0.69	1.69	215	**0.016**
CNS	Spain	Post	1.85	0.23	1.63	2.08	1202	
CNS	United Kingdom	Pre	1.67	0.34	1.33	2.00	480	0.209
CNS	United Kingdom	Post	1.89	0.33	1.56	2.22	1657	
Genitourinary	France	Pre	0.18	0.06	0.12	0.24	49	0.775
Genitourinary	France	Post	0.17	0.07	0.10	0.24	157	
Genitourinary	Germany	Pre	0.26	0.10	0.16	0.36	91	0.287
Genitourinary	Germany	Post	0.20	0.10	0.10	0.30	248	

Genitourinary	Italy	Pre	0.19	0.07	0.12	0.26	52	0.101
Genitourinary	Italy	Post	0.26	0.10	0.16	0.35	212	
Genitourinary	Spain	Pre	0.25	0.16	0.08	0.41	41	0.070
Genitourinary	Spain	Post	0.40	0.06	0.33	0.46	257	
Genitourinary	United Kingdom	Pre	0.31	0.11	0.21	0.42	85	0.151
Genitourinary	United Kingdom	Post	0.23	0.09	0.14	0.33	209	
Infectious disease	France	Pre	0.86	0.16	0.70	1.02	250	**0.007**
Infectious disease	France	Post	1.23	0.35	0.88	1.58	1109	
Infectious disease	Germany	Pre	0.80	0.26	0.54	1.06	270	0.220
Infectious disease	Germany	Post	0.97	0.28	0.69	1.25	328	
Infectious disease	Italy	Pre	0.87	0.24	0.63	1.12	216	0.162
Infectious disease	Italy	Post	1.09	0.39	0.70	1.48	908	
Infectious disease	Spain	Pre	1.24	0.26	0.98	1.50	265	**0.016**
Infectious disease	Spain	Post	1.73	0.53	1.21	2.26	1108	
Infectious disease	United Kingdom	Pre	1.03	0.21	0.82	1.23	284	**0.004**
Infectious disease	United Kingdom	Post	1.44	0.32	1.13	1.76	1251	
Metabolic	France	Pre	0.81	0.33	0.48	1.13	214	0.442
Metabolic	France	Post	0.92	0.18	0.74	1.11	851	
Metabolic	Germany	Pre	0.96	0.47	0.49	1.43	308	0.112
Metabolic	Germany	Post	1.33	0.27	1.06	1.60	1540	
Metabolic	Italy	Pre	0.84	0.42	0.42	1.25	200	0.217
Metabolic	Italy	Post	1.08	0.17	0.91	1.25	896	
Metabolic	Spain	Pre	0.98	0.40	0.58	1.37	189	0.136
Metabolic	Spain	Post	1.27	0.26	1.01	1.52	835	
Metabolic	United Kingdom	Pre	1.28	0.35	0.93	1.63	353	0.194
Metabolic	United Kingdom	Post	1.50	0.24	1.27	1.74	1318	
Oncology	France	Pre	2.37	0.59	1.78	2.97	687	**0.001**
Oncology	France	Post	3.87	0.77	3.10	4.64	3487	
Oncology	Germany	Pre	2.15	0.49	1.66	2.64	808	0.058
Oncology	Germany	Post	2.69	0.59	2.10	3.28	3075	
Oncology	Italy	Pre	2.93	0.72	2.21	3.66	755	0.078
Oncology	Italy	Post	3.64	0.78	2.86	4.42	3030	
Oncology	Spain	Pre	2.38	0.75	1.64	3.13	460	**0.001**
Oncology	Spain	Post	4.63	1.10	3.52	5.73	2944	
Oncology	United Kingdom	Pre	2.51	0.56	1.95	3.07	703	**0.020**
Oncology	United Kingdom	Post	3.35	0.80	2.55	4.14	2895	
Ophthalmology	France	Pre	0.10	0.07	0.04	0.17	26	Not determined
Ophthalmology	France	Post	0.21	0.04	0.17	0.25	184	
Ophthalmology	Germany	Pre	0.10	0.07	0.03	0.17	30	Not determined
Ophthalmology	Germany	Post	0.21	0.06	0.15	0.27	238	
Ophthalmology	Italy	Pre	0.13	0.10	0.03	0.23	23	

Ophthalmology	Italy	Post	0.25	0.05	0.20	0.31	207	Not determined
Ophthalmology	Spain	Pre	0.13	0.08	0.05	0.22	24	Not determined
Ophthalmology	Spain	Post	0.31	0.06	0.25	0.36	194	
Ophthalmology	United Kingdom	Pre	0.15	0.06	0.09	0.20	37	**0.001**
Ophthalmology	United Kingdom	Post	0.28	0.08	0.20	0.36	242	
Vaccines	France	Pre	0.11	0.05	0.06	0.16	26	Not determined
Vaccines	France	Post	0.16	0.09	0.07	0.25	147	
Vaccines	Germany	Pre	0.22	0.10	0.12	0.32	68	0.852
Vaccines	Germany	Post	0.21	0.10	0.11	0.31	256	
Vaccines	Italy	Pre	0.13	0.06	0.07	0.19	29	Not determined
Vaccines	Italy	Post	0.13	0.09	0.05	0.22	117	
Vaccines	Spain	Pre	0.13	0.06	0.07	0.18	30	Not determined
Vaccines	Spain	Post	0.25	0.07	0.17	0.32	163	
Vaccines	United Kingdom	Pre	0.22	0.11	0.11	0.33	53	0.049
Vaccines	United Kingdom	Post	0.34	0.11	0.23	0.45	301	

Source: Trialtrove and Pharmaprojects. Mean number of clinical trials starting each year in each phase in each analysis region and country, and standard deviations, were determined for both the pre and post periods. Shapiro-Wilk tests were conducted to check data distribution prior to parametric (Welch's t-test) tests for significance between the pre and post groups. Significant differences between the pre and post periods are highlighted in bold.

Interpretation of possible causes for changes in IEC-9

In summary, IEC-9 aims to assess differences in productivity across the EU following the implementation of the general pharmaceutical legislation with regards to the number of clinical trials conducted. For Phase 1 trials, the vast majority of countries were shown to increase in productivity (number of Phase 1 clinical trials starting each year), so any impact of the implementation of the general pharmaceutical legislation seems to have been evenly distributed across the EU with regards to Phase 1 trials. However, Phase 1 trials tend to take place in a single country, and sometimes at single sites, in a small number of healthy volunteers to establish safety, so they should be considered the least important measure of productivity, as drug efficacy is not established in such trials. At Phase 2 and Phase 3, the majority of the larger countries in the EU saw significant increases in the numbers of trials started each year in the post period compared to the pre period, and the remaining countries saw comparative numbers. This is most likely due to the favouring of the larger, more attractive markets for initial approval (whether a drug is approved via the centralised or decentralised procedure), and the fact that larger countries are more attractive for recruiting patients for larger trials due to the expected higher numbers of eligible patients.

IEC-10: Revenue generated by pharma companies

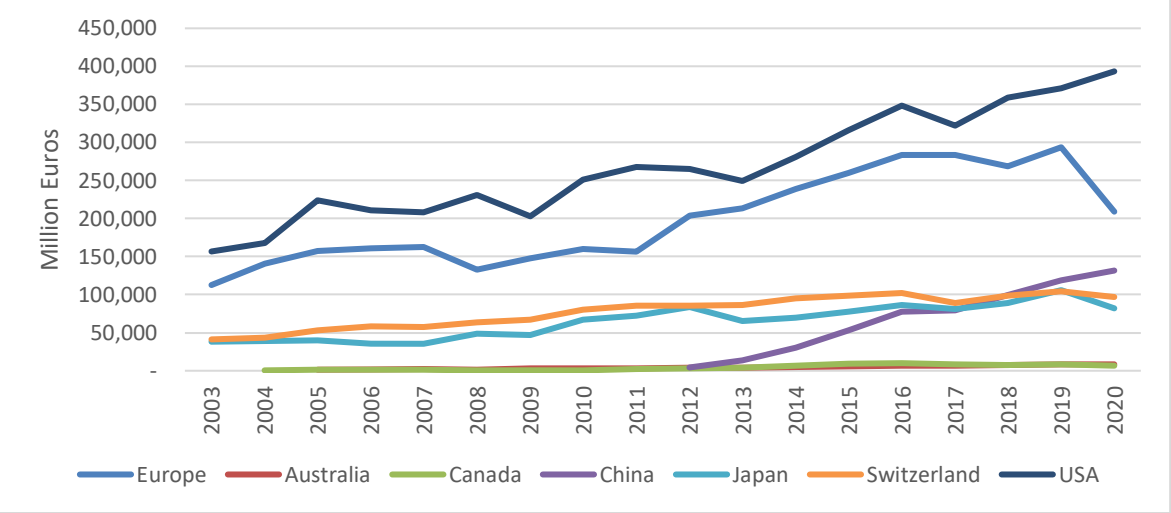
Indicators IEC-10 and IEC-11 are constructed from the EU and World Industrial R&D Investment Scoreboard (IRI, available at https://iri.jrc.ec.europa.eu/data) data. The EU Industrial R&D Investment Scoreboard, compiled by the European Commission's Joint Research Centre, collects data on the largest corporate R&D investors, based on the companies' annual reports. The latest data covers top 1000 companies (across all sectors) in the EU Industrial R&D Investment Scoreboard and top 2500 companies (across all sectors) in World Industrial R&D Investment Scoreboard

Since our focus is on pharmaceutical companies, we only analysed data on the subset

of firms in the sector "Pharmaceuticals & Biotechnology". Figure IEC-10 and Figure IEC-11 are based on an average of 120 Europe based companies that reported information during 2003-2020 and 183 companies based on Australia (1%), Canada(2%), China(17%), Japan(13%), Switzerland(4%), and USA(71%). Pharmaceutical companies constitute around 13% of the world's largest spenders on research. The largest companies in terms of total R&D spending in the data are Roche, Johnson & Johnson, Pfizer, Novartis, and GlaxoSmithKline.

Figure IEC-10 plots the total annual revenues of pharmaceutical companies in the respective regions (without adjustment for inflation). The differences in the level of total revenues mainly reflect size effects due to the different numbers of firms included. Differences in level of revenues aside, the growth rates of Europe, China and US are the highest and similar in particular since 2013 when there is data available for China. The average annual growth rate is 4.6% for Europe during the entire period and 6.1% for the US. Switzerland and Japan also follow similar paths with more moderate growth rates than the first three jurisdictions. Finally, Canada and Australia experience the lowest growth rates across all jurisdictions. Overall, there is no evidence that the reforms introduced by the EU General Pharmaceutical Legislation had an impact on the trend observed for pharmaceutical revenues after 2005.

Figure IEC-10: Revenue generated by pharma companies

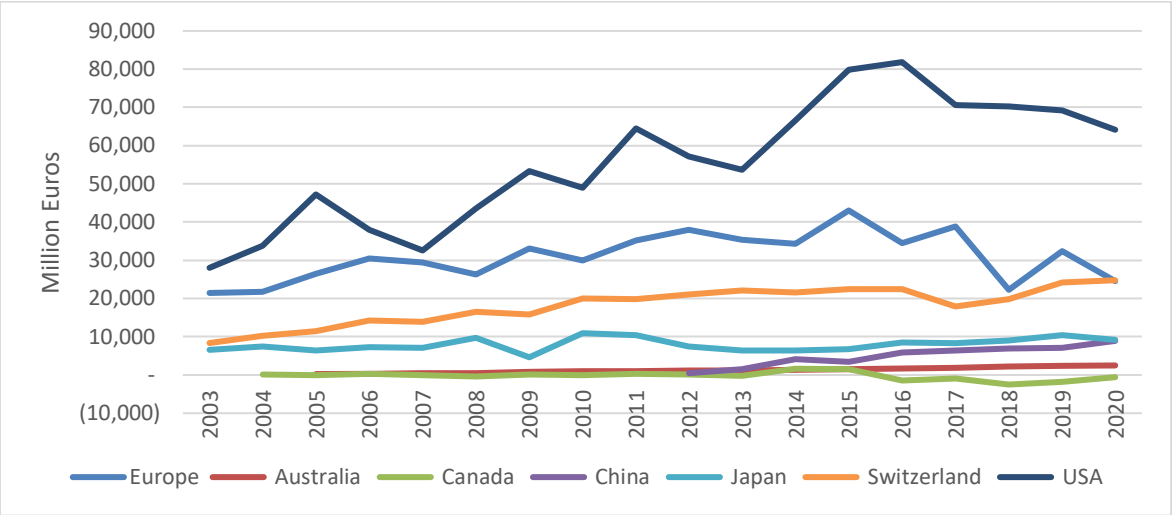


Source: EU and World Industrial R&D Investment Scoreboard. The latest data covers top 1000 companies in the EU Industrial R&D Investment Scoreboard and top 2500 companies in World Industrial R&D Investment Scoreboard. Figures have not been adjusted by inflation.

IEC-11: Gross profit

Figure IEC-11 plots the aggregated annual profits of pharmaceutical companies in the respective regions. The US and Europe appear on top with US experiencing average annual growth rates of 6.6% in profits during 2003-2020 relative to 3.1% in Europe. The lower growth rates in Europe are influenced by a marked reduction in profits during 2016-2020. This extended period of decline in Europe is not observed in Switzerland or Japan. While Canadian companies reported negative profits during the same period (2016-2020). Just as with Figure IEC-10, there is no evidence that the reforms introduced by the EU General Pharmaceutical Legislation had an impact on the trend observed for pharmaceutical profits after 2005.

Figure IEC-11: Profits generated by pharma companies

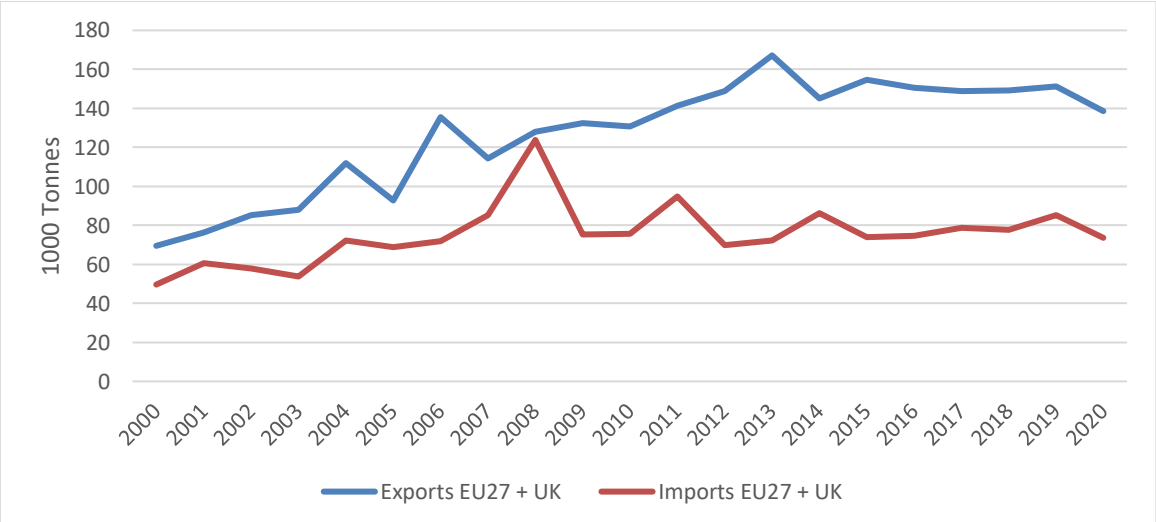


Source: EU and World Industrial R&D Investment Scoreboard. The latest data covers top 1000 companies in the EU Industrial R&D Investment Scoreboard and top 2500 companies in World Industrial R&D Investment Scoreboard. Figures have not been adjusted by inflation.

IEC-12: Volumes of EU import/export of APIs, vaccines, finished pharmaceutical products and antibiotics

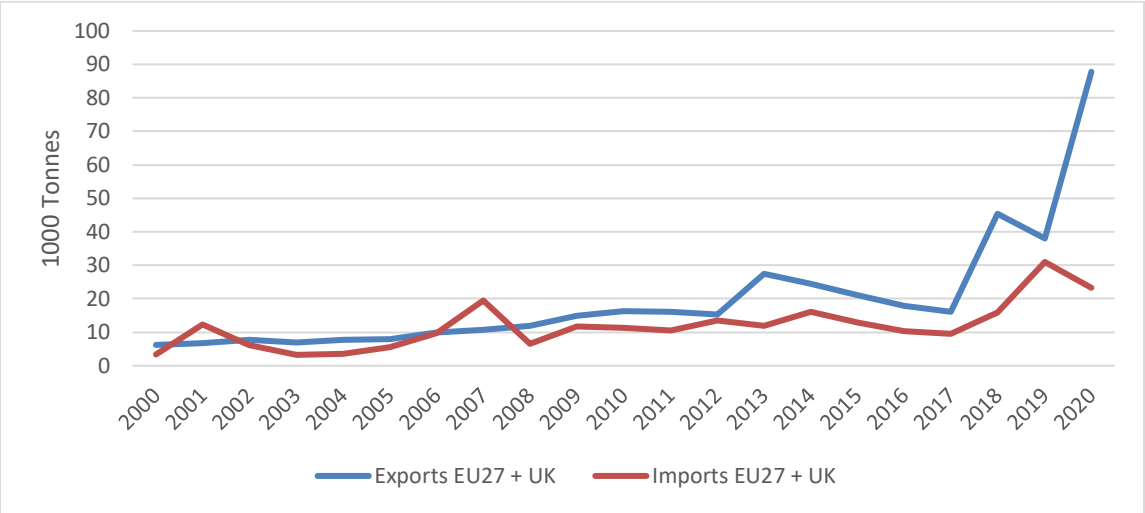
In terms of **antibiotics finished pharmaceutical products** (FPPs), EU28 export volumes have shown a steady growth from 2000 until 2013 when they seem to have stalled (Figure IEC-12.1). On the other hand, EU28 imports volume for antibiotics FPPs had a significant growth in 2007 and 2008 where they reached the highest point during the period 2000-2020. Something similar happened with the volume of EU28 **vaccines** imports, which peaked in 2007 and then again in 2019, while exports peaked in 2020 probably due to the COVID-19 pandemic (Figure IEC-12.2). On the other hand, import volumes of EU28 **finished pharmaceutical products** (FPPs) peaked in 2004 and 2009 (Figure IEC-12.3). Finally, EU28 **APIs** exports and imports from and to all countries of the world both displayed constant growth during 2000-2020 without any major changes in their trends (Figure IEC-12.4).

Figure IEC-12.1: Antibiotics FPPs exports and imports (volumes, tonnes)



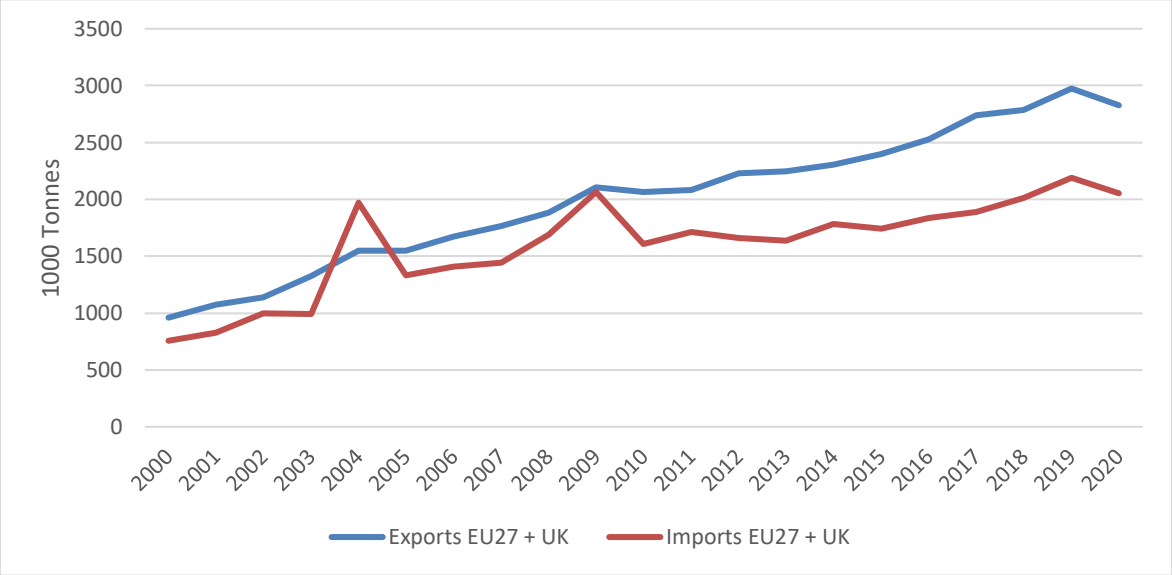
Source: Eurostat. EU28 (EU27 and UK) antibiotics exports (imports) to (from) all countries of the world. Antibiotics FPPs correspond the 2 products listed in the Annex of the EFPIA-ECIPE report "Key Trade Data Points on the EU27 Pharmaceutical Supply Chain" published in July 2020. See Annex B for the complete list of product types.

Figure IEC-12.2: Vaccines exports and imports (volumes, tonnes)



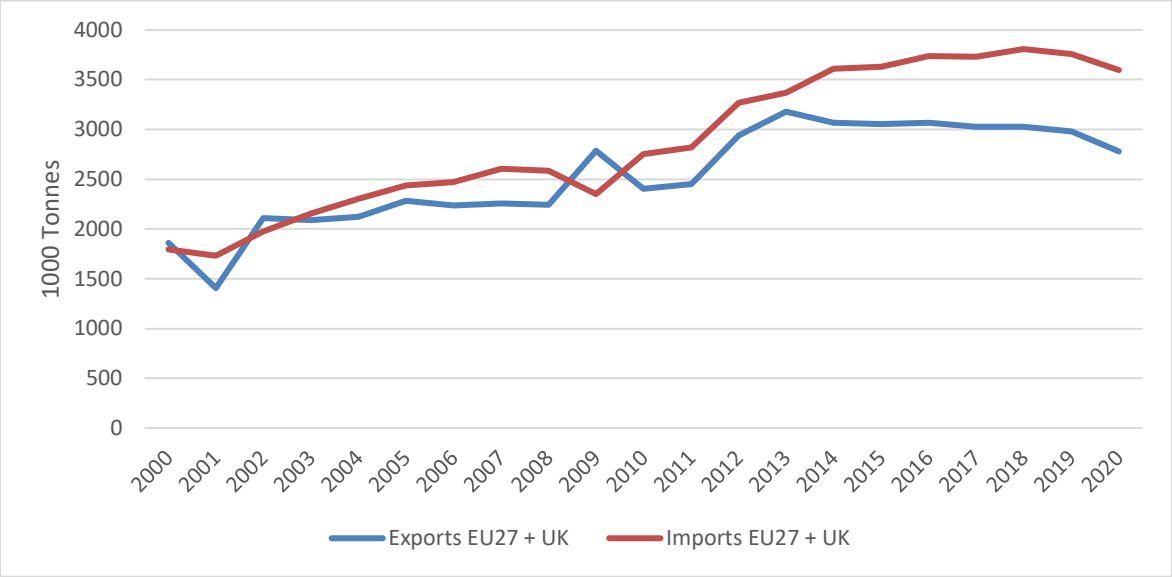
Source: Eurostat. EU28 (EU27 and UK) vaccines exports (imports) to (from) all countries of the world. Vaccines correspond to code 300220 as described in the Annex of the EFPIA-ECIPE report "Key Trade Data Points on the EU27 Pharmaceutical Supply Chain" published in July 2020. See Annex B for the complete list of product types.

Figure IEC-12.3: FPPs exports and imports (volumes, tonnes)



Source: Eurostat. EU28 (EU27 and UK) FPPs exports (imports) to (from) all countries of the world. FPPs correspond to the 13 products listed in the Annex of the EFPIA-ECIPE report "Key Trade Data Points on the EU27 Pharmaceutical Supply Chain" published in July 2020. See Annex B for the complete list of product types.

Figure IEC-12.4: API exports and imports (volumes, tonnes)

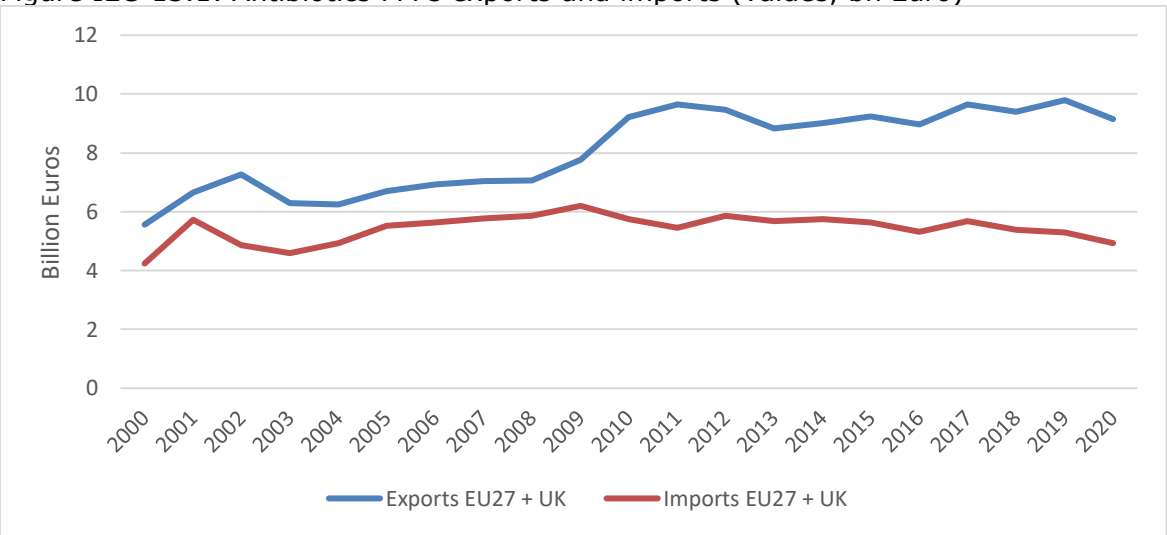


Source: Eurostat. EU28 (EU27 and UK) APIs exports (imports) to (from) all countries of the world. Active Pharmaceutical Ingredients include the 101 products listed in the Annex of the EFPIA-ECIPE report "Key Trade Data Points on the EU27 Pharmaceutical Supply Chain" published in July 2020. See Annex B for the complete list of product types.

IEC-13: Values of EU import/export of APIs, vaccines, finished pharmaceutical products and antibiotics

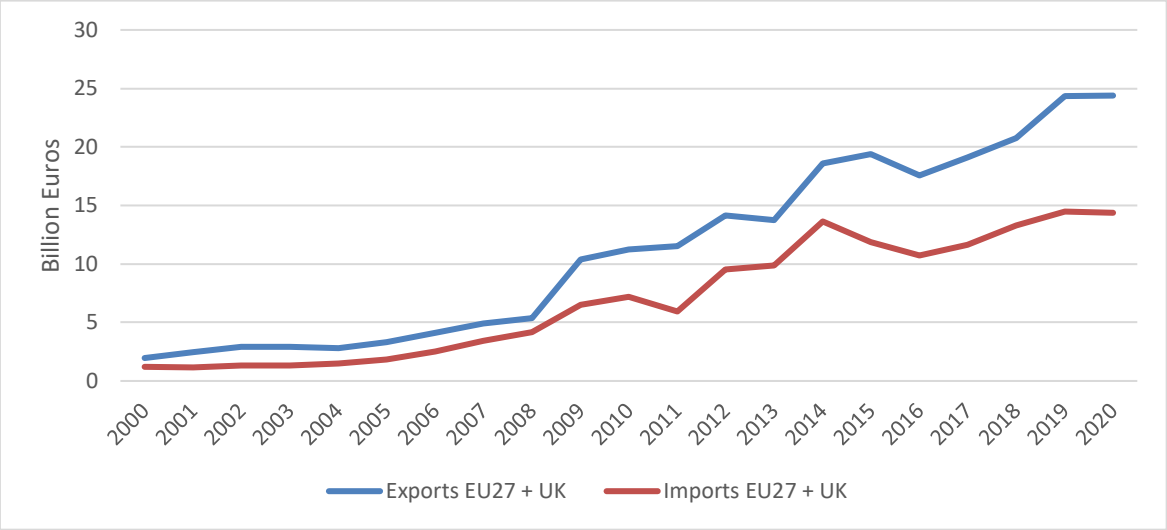
In terms of value, EU28 **antibiotics** finished pharmaceutical products (FPPs) exports have shown an important growth from 2008 until 2011 when they seem to have stalled just as with the graph representing volumes. On the other hand, EU28 imports values for antibiotics FPPs reached their highest point in 2008 just as with the graph representing volumes (Figure IEC-13.1).
EU28 **vaccines** imports and exports values display high growth rates, in particular since 2008 (Figure IEC-13.2), while import and export values for overall FPPs and APIs have also displayed more consistent growth rates between 2000-2020 (Figures IEC-13.3 and IEC-13.4).

Figure IEC-13.1: Antibiotics FPPs exports and imports (values, bn Euro)



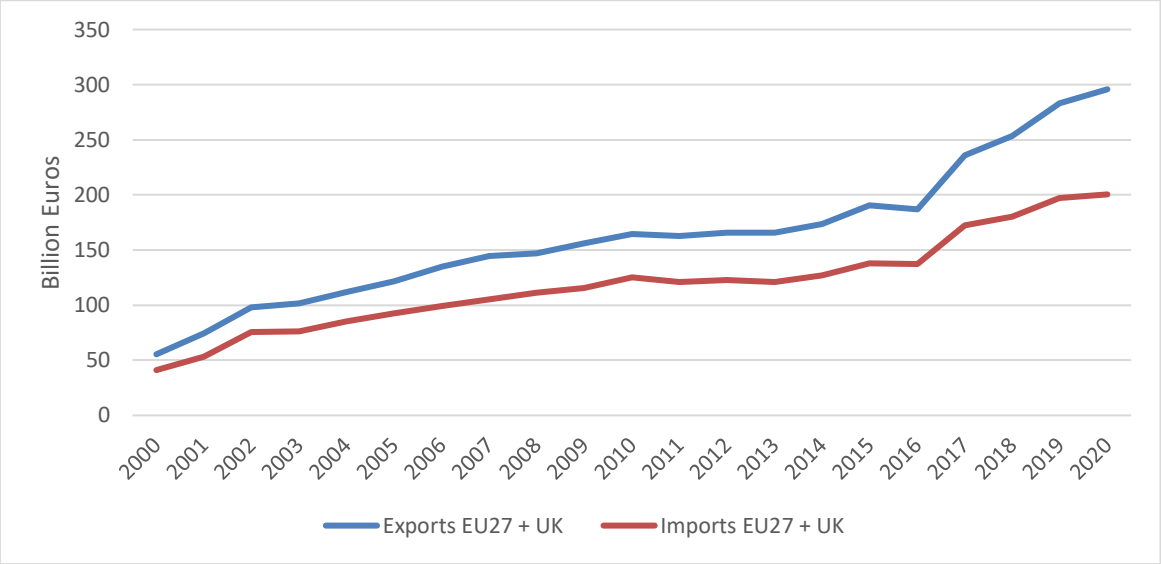
Source: Eurostat. EU28 (EU27 and UK) Antibiotics FPPs exports (imports) to (from) all countries of the world. Antibiotics FPPs include the 2 products listed in the Annex of the EFPIA-ECIPE report "Key Trade Data Points on the EU27 Pharmaceutical Supply Chain" published in July 2020. See Annex B for the complete list of product types. Figures are not adjusted for inflation.

Figure IEC-13.2: Vaccines exports and imports (values, bn Euro)



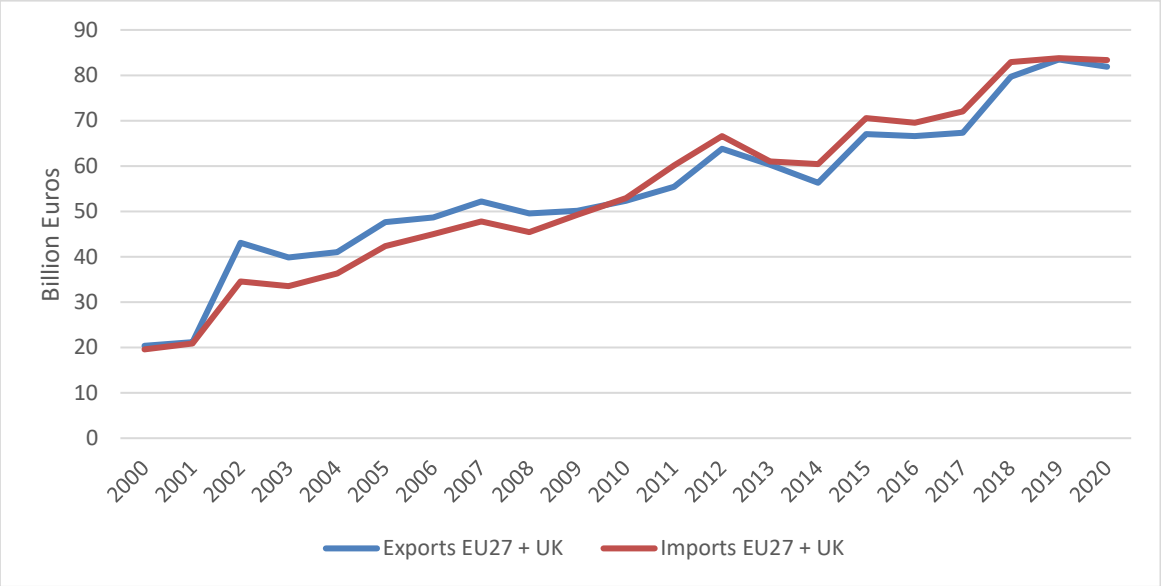
Source: Eurostat. EU28 (EU27 and UK) vaccines exports (imports) to (from) all countries of the world. Vaccines correspond to code 300220 as described in the Annex of the EFPIA-ECIPE report "Key Trade Data Points on the EU27 Pharmaceutical Supply Chain" published in July 2020. Figures are not adjusted for inflation.

Figure IEC-13.3: FPPs exports and imports (values, bn Euro)



Source: Eurostat. EU28 (EU27 and UK) FPPs exports (imports) to (from) all countries of the world. Finished Pharmaceutical Products include the 13 products listed in the Annex of the EFPIA-ECIPE report "Key Trade Data Points on the EU27 Pharmaceutical Supply Chain" published in July 2020. See Annex B for the complete list of product types. Figures are not adjusted for inflation.

Figure IEC-13.4: API exports and imports (values, bn Euro)



Source: Eurostat. EU28 (EU27 and UK) APIs exports (imports) to (from) all countries of the world. Active Pharmaceutical Ingredients include the 101 products listed in the Annex of the EFPIA-ECIPE report "Key Trade Data Points on the EU27 Pharmaceutical Supply Chain" published in July 2020. See Annex B for the complete list of product types. Figures are not adjusted for inflation.

1.2 RESEARCH & INNOVATION INDICATORS

The pharmaceutical industry is highly research intensive, with firms active across all phases of the R&D lifecycle, making the largest contribution to translating and applying knowledge to develop products. The industry invests particularly heavily in the clinical trials required to generate data to obtain marketing authorisation. There was an assumption that the 2004 revisions of the EU general pharmaceutical legislation would enhance the global attractiveness to catalyse increased R&D activities to develop innovative products and ultimately leading to the authorisation of new medicines in Europe. The following indicators were developed to provide quantitative evidence supporting the evaluation of the 2004 revision of the general pharmaceutical legislation.

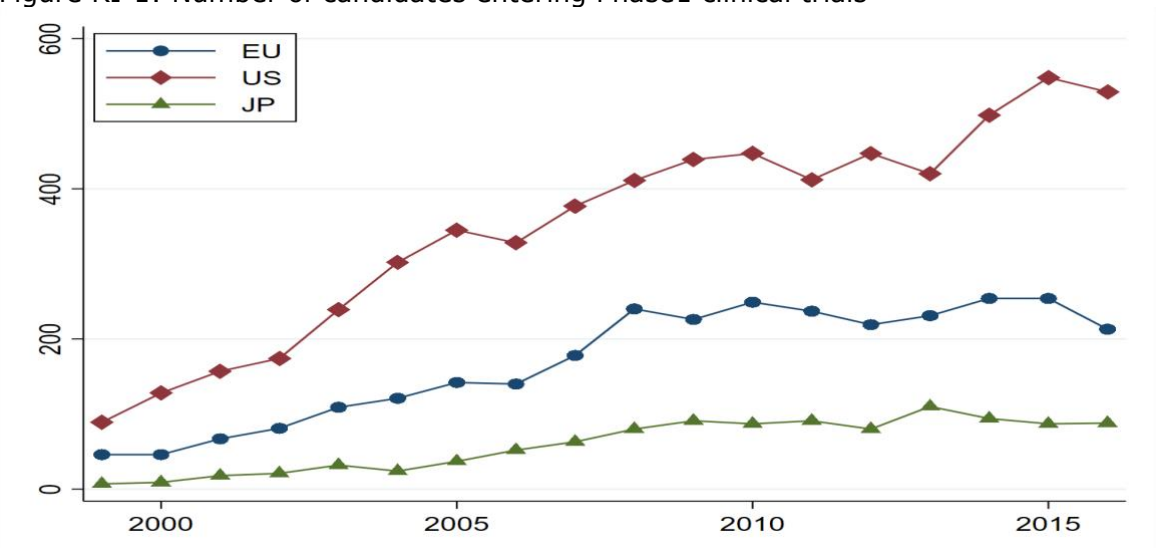
Indicator name	Indicator description
	Conversion rates:
RI-1	Number of candidates entering Phase 1 clinical trials
RI-2	Transition success rate (%) of candidates from Phase 1 to Phase 2 clinical trials
RI-3	Transition success rate (%) of candidates from Phase 2 to Phase 3 clinical trials
RI-4	Transition success rate (%) of candidates from Phase 3 to approval
RI-6	Overall Likelihood of Approval (LOA) from Phase 1
	Public research funding:
RI-7	Number of grants and value of grant funding by country and/or funding body
	Private R&D investment:
RI-8	Amount of private R&D investment in the sector
	Innovative products:
RI-9	Number of innovative medicines

Note that RI-5 involved the transition from application to approval, but it was possible to measure this due to the lack of systematic data published on applications for marketing authorisation. Therefore, the step from Phase 3 to approval (RI-4) cannot be broken down to examine the transition from application to approval.

RI-1: Number of candidates entering Phase1 clinical trials

RI-1 counts the number of candidate medicinal products entering Phase 1 clinical testing in the EU, the USA, and Japan, respectively. Since data availability is scarce until the late 1990s and in the most recent years, we limit the analysis to the 1999-2016 period. The figure below illustrates that the number of candidates has increased over time. In the period after 2004, between 300 and 600 Phase 1 candidates are tested annually in the USA, between 150 and 250 in the EU, and between 40 and 110 in Japan.

Figure RI-1: Number of candidates entering Phase1 clinical trials



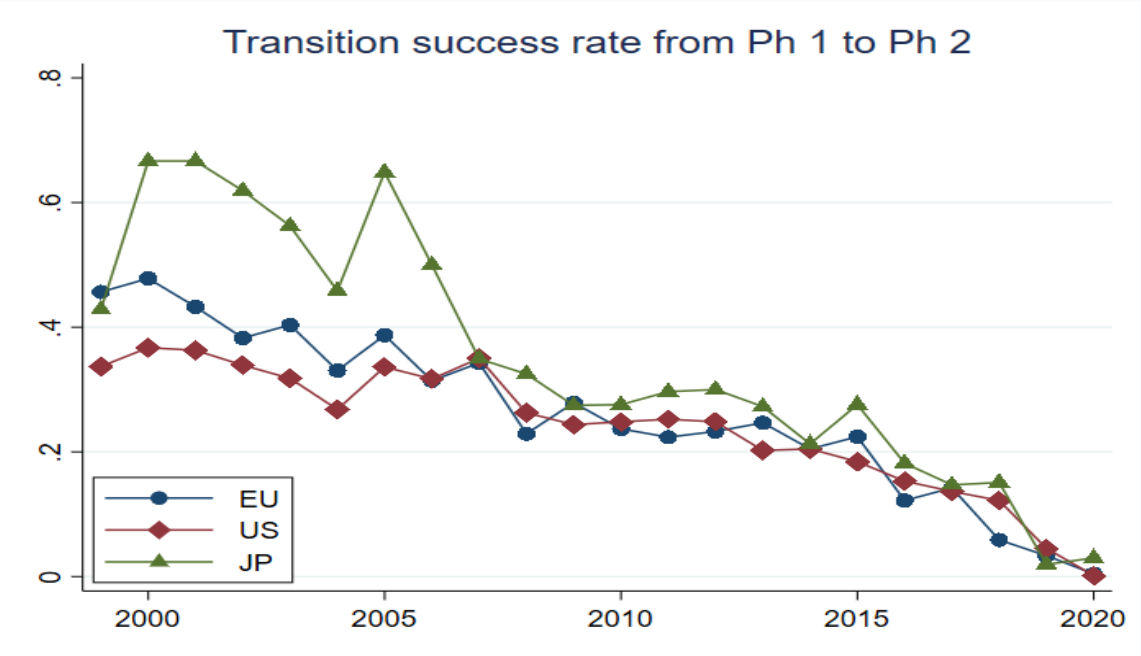
Source: Trialtrove and Pharmaprojects. We consider that a Phase 1 trial in time t-1 was completed successfully if a candidate medicinal product is observed in a Phase 2 trial in time t. The third and final phase is considered as completed successfully if the medicinal product is observed as being approved for sale in time t+1. The final dataset contains a total of 13,849 Phase 1 trials, 16,484 Phase 2 trials, and 8,168 Phase 3 trials.

RI-2: Transition success rate (%) of candidates from Phase 1 to Phase 2 clinical trials

RI-2 indicates the share of Phase 1 candidate drugs that successfully transition to Phase 2 clinical trials. Again, we differentiate by geographic region and limit the analysis to the 1999-2016 period. Still, the time series for Japan remains rather volatile, particularly in early periods.

We count a Phase 1 trial as completed successfully if we observe a subsequent Phase 2 trial for the same candidate medicinal product in the same indication. Thus, the likelihood of success is expected to decrease towards the end of the sample period, because it is less likely that we observe subsequent trials in the dataset. Yet, we observe a decrease in the Phase 1 success rate over the entire sample period, dropping from about 40% before 2005 to about 20% in the period after, which is indicative of the decrease in research productivity for the pharmaceutical industry in the last two decades (an alternative explanation would be an increased willingness on the part of pharmaceutical companies to terminate drugs early in the development process before too many resources are expended). Noticeably, the probability of a successful Phase 1 clinical trial is higher for Japanese trials than in the other two regions.

Figure RI-2: Transition success rate (%) of candidates from Phase 1 to Phase 2 clinical trials



Source: Trialtrove and Pharmaprojects.

Next, we conduct a regression analysis of successful Phase 1 trials, following a difference-in-differences setup: comparing the EU to the USA and Japan before and after the implementation of the 2004 revision of the general pharmaceutical regulations gives us an estimate of the change in the likelihood of trial success in the EU vis-à-vis the other regions and the pre-2005 period. In all regressions, it is important to account for year fixed-effects (and potentially other confounders), to account for the decrease in the likelihood of success over time.

The table below contains the results for three different regression setups. In column (1), we control for year fixed-effects, as well as for the composition of trial sponsors. Trials can be conducted by academic units, government researchers, or pharmaceutical firms – which we further divide into large (top 20) and small (the rest). Controlling for sponsors is akin to keeping the composition of sponsors constant across jurisdictions. In column (2), we add fixed-effects for therapy areas, accounting for the fact that the different regions might be focused on research in different areas. Finally, column (3) contains the same control variables as column (2), but dissects the average treatment effect (ATE) on a yearly basis. Thus, instead of reporting an overall impact for the post-2004 period, column (3) estimates a different coefficient for each year in the post period.

Table RI-2: transition success rate (%) of candidates from Phase 1 to Phase 2 clinical trials

	(1)		(2)		(3)	
ATE	-0.042*	(-1.92)	-0.050**	(-2.31)		
2005					-0.015	(-0.35)
2006					-0.052	(-1.18)
2007					-0.036	(-0.90)
2008					-0.085**	(-2.32)
2009					-0.024	(-0.65)
2010					-0.054	(-1.49)
2011					-0.068*	(-1.85)
2012					-0.055	(-1.48)
2013					-0.004	(-0.12)
2014					-0.038	(-1.07)

2015			-0.022	(-0.62)
2016			-0.069*	(-1.88)
2017			-0.050	(-1.38)
2018			-0.124***	(-3.30)
2019			-0.042	(-1.04)
2020			-0.025	(-0.69)
N	13847	13847	13847	

t statistics in parentheses. Column (1) contains fixed-effects for years and sponsor types; column (2) adds fixed-effects for indications. Column (3) estimates separate treatment effects for each post period. * p < 0.1, ** p < 0.05, *** p < 0.01

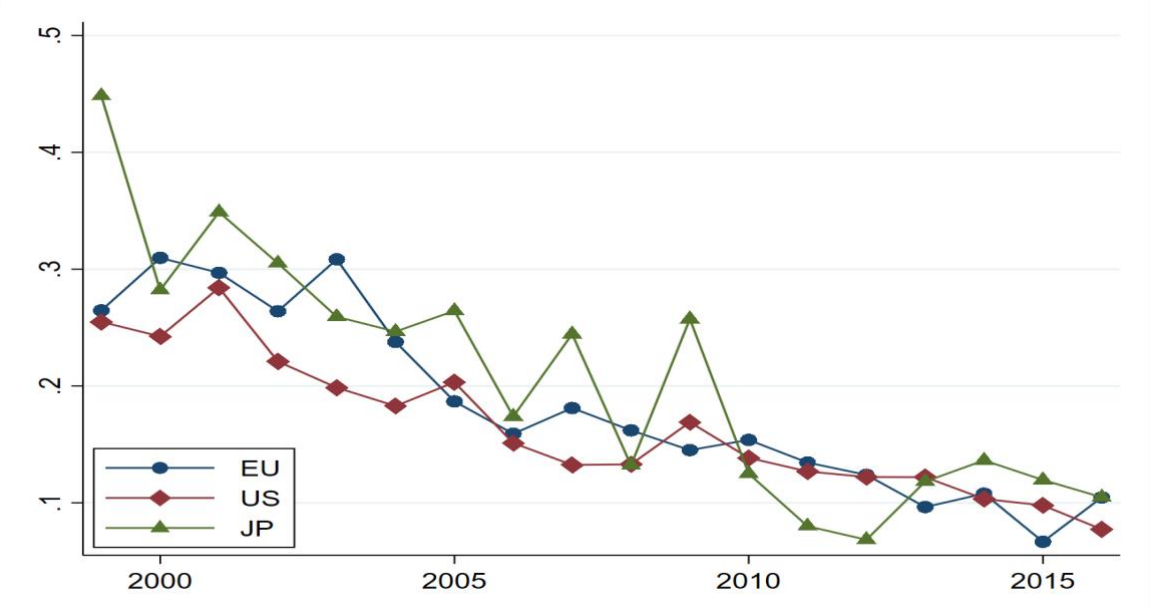
The results show that the probability of successful Phase 1 trials (as captured by the coefficient ATE) decreased in the EU, relative to the USA and Japan, and relative to the pre-2005 period. In column (1), the effect is only weakly significant and indicates a decrease of 4 percentage points. In column (2), the effect size increases to 5 percentage points, as does the significance. Finally, column (3) shows that the effect is not constant across time periods. While the estimates are negative for all individual years from 2005 onwards, only few coefficients are statistically significant. The largest effect is observed in 2018, when the likelihood of success of Phase 1 trials drops by 12.4 percentage points in the EU.

Thus, in terms of successfully completed Phase 1 trials, the EU seems to have underperformed relative to the US and Japan.

RI-3: Transition success rate (%) of candidates from Phase 2 to Phase 3 clinical trials

RI-3, similarly, indicates the share of successfully completed Phase 2 trials, which we infer from the observation of subsequent Phase 3 trials. The same caveats apply as for RI-2. Again, we see the probability of success decline over time. While the average success rate before 2005 oscillates between 20% and 30%, it drops to around 10% after. As before, Japanese trials seem to exhibit a higher success rate than the USA or the EU.

Figure RI-3: transition success rate (%) of candidates from Phase 2 to Phase 3 clinical trials



The regression analysis of successful Phase 2 trials follows the same approach as the analysis of Phase 1 trials above; results are collected in the table below. Again, we

observe a decrease in the likelihood of success in the EU vis-à-vis the other regions. Columns (1) and (2) indicate a decrease of around 4 percentage points, significant at the 1% level. Column (3) shows that the decrease is up to 7 or 8 percentage points in specific periods (2009 and 2013, but also 2015 and 2017), while being insignificant and close to zero in others (2007, 2008, 2011, and 2018).

Table RI-3: transition success rate (%) of candidates from Phase 2 to Phase 3 clinical trials

	(1)		(2)		(3)	
ATE	-0.043***	(-3.25)	-0.041***	(-3.14)		
2005					-0.056**	(-2.02)
2006					-0.040	(-1.45)
2007					-0.009	(-0.32)
2008					-0.009	(-0.34)
2009					-0.081***	(-3.15)
2010					-0.024	(-0.90)
2011					-0.017	(-0.62)
2012					-0.027	(-0.95)
2013					-0.071**	(-2.56)
2014					-0.036	(-1.29)
2015					-0.068**	(-2.37)
2016					-0.029	(-1.07)
2017					-0.067**	(-2.39)
2018					-0.016	(-0.55)
2019					-0.052*	(-1.76)
2020					-0.032	(-1.29)
N	16484		16484		16484	

t statistics in parentheses. Column (1) contains fixed-effects for years and sponsor types; column (2) adds fixed-effects for indications. Column (3) estimates separate treatment effects for each post-period. * $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

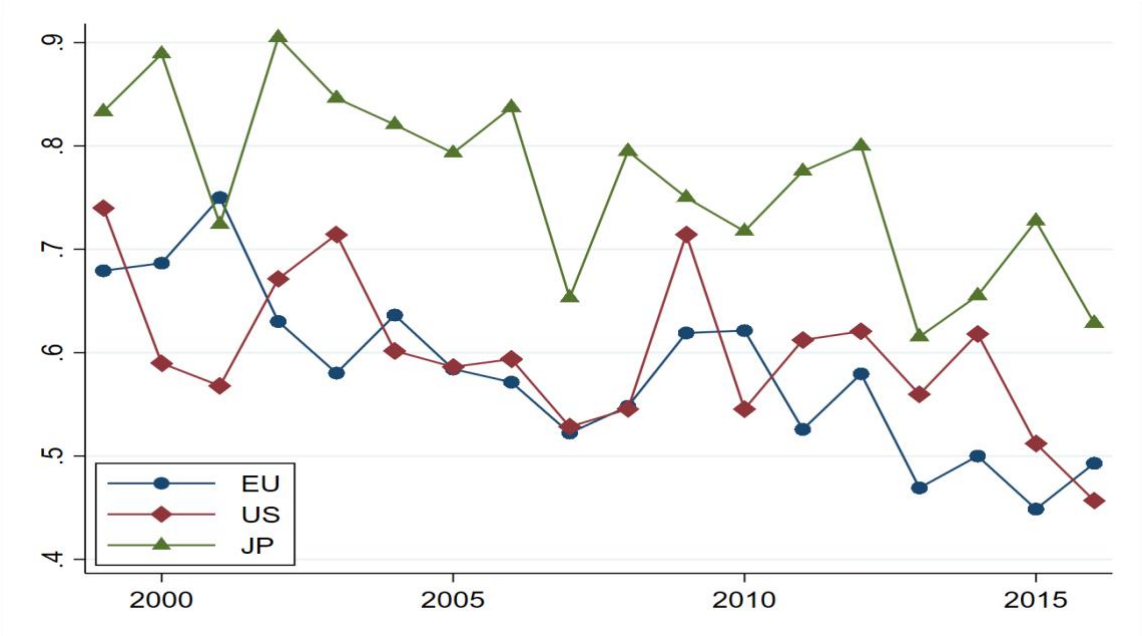
Thus, in terms of successfully completed Phase 2 trials, the EU seems to have underperformed relative to the US and Japan.

RI-4: Transition success rate (%) of candidates from Phase 3 to approval

RI-4 represents the share of candidate medicinal products entering Phase 3 trials that later end up being approved for marketing. The approval year of a drug is merged from the Informa Pharma Pharmaprojects database. We thus calculate the share of medicines in Phase 3 trials that end up being approved for marketing later, and differentiate the three regions of interest: the EU, the USA, and Japan. Note that the approval date is not available for combinatorial drug treatments. Thus, in the following, we focus on single-drug trials.

Once more, we observe that the probability of success declines over time, but to a much smaller extent compared to Phase 1 and Phase 2 trials. The likelihood of success is around 65% before 2005 (and more than 80% in Japan), and declines to around 50% (67% in Japan) after. The likelihood of success is higher for Japanese trials in almost all individual time periods, as can be seen in the figure below.

Figure RI-4: transition success rate (%) of candidates from Phase 3 to approval



Turning to the regression analysis of successful Phase 3 trials, we again follow the setup described above and report the findings in the table below. While the ATEs estimated in columns (1) and (2) are negative, neither of the two is significantly different from zero. Thus, the probability of successfully completing a Phase 3 trial did not decrease in the EU, relative to the other regions and the pre-2005 period.

In column (3), we see that the effect is also insignificant for the individual years between 2005 and 2019. The negative impact in 2020 is likely due to a significant increase in approval of Japanese drugs in 2020 and not due to any effects in the EU.

Table RI-4: transition success rate (%) of candidates from Phase 3 to approval

	(1)		(2)		(3)	
ATE	-0.037	(-1.23)	-0.036	(-1.21)		
2005					0.007	(0.11)
2006					-0.058	(-0.95)
2007					0.020	(0.29)
2008					-0.013	(-0.21)
2009					-0.057	(-0.84)
2010					0.070	(1.08)
2011					-0.082	(-1.24)
2012					-0.022	(-0.32)
2013					-0.082	(-1.19)
2014					-0.100	(-1.42)
2015					-0.075	(-1.08)
2016					0.028	(0.38)
2017					-0.057	(-0.74)
2018					0.040	(0.51)
2019					-0.031	(-0.40)
2020					-0.141**	(-2.13)
N	5117		5117		5117	

t statistics in parentheses. Column (1) contains fixed-effects for years and sponsor types; column (2) adds fixed-effects for indications. Column (3) estimates separate treatment effects for each post-period. * $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

Thus, in terms of successfully completed Phase 3 trials, the EU seems to have performed at a comparable level to the US and Japan.

RI-6: Overall likelihood of approval from Phase 1

RI-6 is similar to RI-4 in that it records success as the approval for a candidate medicinal product to be marketed. It differs from RI-4 insofar that it not only records successful Phase 3 trials, but instead looks at the overall success rate for any candidate in our data (irrespective of the trial phase) to be eventually approved. It is thus correctly interpreted as the share of drugs starting clinical trials in a given year, which later end up being approved for marketing.

The figure below illustrates the overall likelihood of approval in the three regions over time. The likelihood of approval declines until 2005 and remains relatively stable (or declines slightly due to end-of-sample data restrictions) after. Once more, Japanese trials appear to be more successful across the whole sample period.

Figure RI-6: Overall likelihood of approval from Phase 1

The regression results reported in the table below show that the overall likelihood of approval in the EU did not significantly change, relative to the other regions. The coefficients in columns (1) and (2) are small and insignificant. In column (3), we see that the probability of success was lower in the EU in some periods (2013 and 2020), but the coefficients change sign across periods, indicating that no systematic relationship emerges.

Table RI-6: overall likelihood of approval from Phase 1

	(1)		(2)		(3)	
ATE	-0.018	(-1.20)	-0.017	(-1.19)		
2005					-0.001	(-0.03)
2006					0.019	(0.67)
2007					-0.006	(-0.20)
2008					-0.004	(-0.14)
2009					0.010	(0.35)
2010					0.028	(0.98)
2011					-0.027	(-0.96)
2012					0.005	(0.16)
2013					-0.056*	(-1.90)
2014					-0.024	(-0.83)
2015					-0.044	(-1.56)
2016					-0.037	(-1.31)
2017					-0.028	(-1.01)
2018					-0.027	(-0.93)

2019			-0.022	(-0.76)
2020			-0.055**	(-2.20)
N	17431	17431	17431	

t statistics in parentheses. Column (1) contains fixed-effects for years and sponsor types; column (2) adds fixed-effects for indications. Column (3) estimates separate treatment effects for each post-period. * p < 0.1, ** p < 0.05, *** p < 0.01

Thus, in terms of the overall likelihood of drug approval for all Phase 1 candidates, the EU seems to have performed at a comparable level to the US and Japan.

Analysis of heterogeneous effects

In the previous section, we reported ATEs that indicated the average effect of the 2004 revision of the general pharmaceutical legislation in the post-2004 period, as well as effects for each year in that period. In this section, we extend our analysis in three dimensions: first, we look at the probabilities for trial success in different therapy areas; second, we examine whether the identity of the trial sponsor plays a role in the success of trials; and third, we distinguish drugs by their modality.

Therapy areas

In the Trialtrove data, we observe which therapy area and disease a medicine is being tested for. While an analysis at the disease level would be too disaggregate, as there are hundreds of diseases in the data, we report ATEs for individual therapy areas in the table below.

There are nine broad therapy areas in the data. Drugs are being developed in the areas of i) oncology, ii) metabolic/endocrinology, iii) cardiovascular, iv) CNS, v) autoimmune/inflammation, vi) genitourinary, vii) infectious diseases, viii) ophthalmology, and ix) vaccines.

Table RI-6.1: Phase transitions and LoA by therapeutic area

	(1) Phase 1	(2) Phase 2	(3) Phase 3	(4) LoA
Oncology	-0.068***	-0.017	0.067	0.023
	(-2.78)	(-1.06)	(1.30)	(1.21)
Metabolic	-0.056*	-0.016	-0.020	-0.033
	(-1.73)	(-0.66)	(-0.41)	(-1.52)
Cardiovascular	-0.030	-0.049*	-0.048	-0.023
	(-0.83)	(-1.93)	(-0.97)	(-0.93)
CNS	-0.076**	-0.057***	-0.045	-0.025
	(-2.51)	(-2.99)	(-1.03)	(-1.26)
Autoimmune	-0.036	-0.058***	-0.079*	-0.036*
	(-1.23)	(-3.02)	(-1.88)	(-1.89)
Genitourinary	-0.028	-0.059	-0.030	-0.063*
	(-0.46)	(-1.55)	(-0.42)	(-1.77)
Infectious Disease	-0.044	-0.062***	-0.084*	-0.019
	(-1.51)	(-2.97)	(-1.83)	(-0.89)
Ophthalmology	-0.066	-0.012	-0.065	-0.047
	(-0.97)	(-0.27)	(-0.76)	(-1.20)
Vaccines	0.006	-0.069*	0.124	0.041
	(0.17)	(-1.94)	(1.58)	(1.28)
N	13847	16484	5117	17431

t statistics in parentheses. * p < 0.1, ** p < 0.05, *** p < 0.01, all regressions contain fixed-effects for years, indications, and sponsors.

It can be observed that the ATEs differ quite substantially across therapy areas, and, in particular, that the negative impact on the success of Phase 1 and Phase 2 trials in the EU – described above – can be attributed to specific areas, while others are not significantly affected.

In particular, the decrease in successful Phase 1 trials in the EU – which was estimated to be around 4-5 percentage points – most strongly and significantly manifests in the areas of oncology and CNS, as well as – to a lesser extent – metabolic diseases (column (1)). While the coefficients for other therapy areas are mostly negative, they are not statistically significant.

From column (2) it becomes apparent that the decreased probability of Phase 2 trial success in the EU can be explained through decreased success in the areas of CNS, autoimmune diseases, and infectious diseases, as well as – at a lower statistical significance – cardiovascular diseases and vaccines. Thus, while the decreased success of Phase 1 trials can be traced back to only 3 therapy areas, Phase 2 trial success decreases for 5 areas.

The impact on the success of Phase 3 trials – for which no significant overall effect was found above – is mixed and mostly insignificant across therapy areas. Only in two areas (autoimmune and infectious diseases) do we observe reductions at a marginal level of statistical significance.

The change in the overall likelihood of drug approval – for which we also found no significant ATE – is insignificant in most therapy areas, but marginally decreases for autoimmune drug trials and genitourinary drug trials.

Thus, when evaluating successful phase transitions and the overall likelihood of approval for individual therapeutic areas, the below become apparent.

i) In Phase 1 transitions, the EU seems to have underperformed relative to the US and Japan in three therapy areas.
ii) In Phase 2 transitions, the EU seems to have underperformed relative to the US and Japan in five therapy areas.
iii) In Phase 3 transitions, the EU seems to have performed at a comparable level to the US and Japan.
iv) In the overall likelihood of approval, the EU seems to have performed at a comparable level to the US and Japan.

Trial sponsors

The Trialtrove data also contain a field with the identity of the trial sponsor(s) and a classification of trial sponsors into four groups. We distinguish trials sponsored by academic research, by government research, and by the research of pharmaceutical companies; in the latter case, we distinguish trials run by the top 20 pharmaceutical companies (according to Informa Pharma's Scrip database) and other pharmaceutical companies. Note that these categories are non-exclusive: the same trial might be run by academic researchers jointly with pharmaceutical companies. Yet, the overlap across sponsor types is limited, as the average trial is run by only 1.2 sponsors. The table below reports regression results for the individual trial phases and for the overall likelihood of approval.

Table RI-6.2 Phase transitions and LoA by trial sponsor

	(1) Phase 1	(2) Phase 2	(3) Phase 3	(4) LoA
Academic	-0.012	-0.002	-0.071**	0.009
	(-0.67)	(-0.14)	(-2.21)	(0.64)
Top 20 pharma	-0.057***	-0.071***	0.058*	-0.039***
	(-2.94)	(-4.65)	(1.65)	(-2.65)
Government	-0.012	0.015	0.164***	0.083***
	(-0.50)	(0.85)	(3.07)	(4.29)
Other pharma	-0.031*	-0.036***	-0.023	-0.001
	(-1.67)	(-2.66)	(-0.74)	(-0.04)
N	13847	16484	5117	17431

t statistics in parentheses. * p < 0.1, ** p < 0.05, *** p < 0.01, all regressions contain fixed-effects for years, indications, and sponsors.

The analysis of sponsor types reveals some interesting heterogeneities. The EU's relative decline in the success of Phase 1 and Phase 2 trials reported above is due to less trial success by pharmaceutical companies. The top 20 firms are particularly affected (with a decrease of almost 6 percentage points in Phase 1 and 7 percentage points in Phase 2 trials), while other pharma firms are somewhat affected (a decrease of 3-4 percentage points). Conversely, the success rates for academic and government run trials did not decline.

In column (3), we see that academic run Phase 3 trials in the EU are almost 7 percentage points less likely to succeed after 2004, relative to the USA and Japan. Surprisingly, we see a large increase of 16 percentage points in the likelihood of success of government run trials. At a baseline success rate of 32% for European Phase 3 trials, this corresponds to a 50% increase.

Finally, column (4) reports the findings for the overall likelihood of approval. Again, we see a large increase in the success rate of government trials, while the success rate of top 20 pharmaceutical companies diminishes modestly. No significant effect is found for academic trials or other pharmaceutical companies.

The increased success in Phase 3 and marketing authorization for government-backed trials in the post period can, to some degree, be explained by changes in the sample composition before and after 2004. Before 2004, more than 30% of trials involving government funding were focused in the indication of oncology. Oncology is, on average, the therapeutic area with the lowest trial success rate, across all regions and periods (29% success vs 34% for all other therapeutic areas). After 2004, the share of government-backed oncology trials in the EU drops to less than 22%. Instead, more focus is being put on therapeutic areas with a higher average success rate (the share of trials for cardiovascular drugs, which enjoy a success rate of more than 42%, has increased from 6% to 9%).

Thus, the increased success of trials involving governmental researchers in the EU after 2004 can partially be explained by a shift away from research in therapeutic areas where success is unlikely, towards those with higher success rates.

The composition of trial sponsors has also changed over time (we observe more trials by other pharma firms; less trials by the government and top 20 pharma firms; and roughly equally many trials involving academic sponsors in the EU after 2004). However, we would not expect this to affect the results: firstly, the outcome is the ratio of successful over total trials and should therefore be robust to size effects. Secondly, the matching analysis below accounts for such difference in composition and yields consistent findings.

Thus, when evaluating successful phase transitions and the overall likelihood of approval by sponsor type, the below become apparent.

i) The relative decline of successful Phase 1 and 2 transitions in the EU can be explained by a decline in the success of trials run by pharmaceutical companies (both large and small).
ii) Government-backed drug trials in the EU are much more likely to successfully complete Phase 3/be approved for marketing after 2004 than their US and Japan counterparts.

Drug modality

As a final dimension of heterogeneity, the data allow us to distinguish drug modalities. We observe seven different modalities in the data: i) small molecule, ii) antibody, iii) cellular therapy, iv) gene therapy, v) RNA, vi) peptide, and vii) fusion protein. While these categories are non-exclusive (such as in the case of antibody fusion proteins), 86% of drugs in the data fall in exactly one category, while 7% fall in none. Thus, only 7% of drugs have more than one modality.

Another important point is the unequal distribution of drugs across modalities. While almost 76% of drugs in the data fall into the small molecule category and almost 13% into the antibody category, only 5% of drugs are cell therapy or gene therapy related. The remaining categories (RNA, peptide, fusion protein) account for around 1% of drugs each. Thus, estimates for those drugs will have a high degree of statistical uncertainty and should be interpreted with caution.

In the table below, we report the ATEs on the probabilities of phase transitions and LoA, disaggregated by drug modality.

Table RI-6.3. Phase transitions and LoA by drug modality

	(1) Phase 1	(2) Phase 2	(3) Phase 3	(4) LoA
Small molecule	-0.040***	-0.022*	-0.087***	-0.029**
	(-2.61)	(-1.94)	(-3.23)	(-2.44)
Antibody	0.026	-0.011	0.048	-0.024
	(1.17)	(-0.70)	(0.84)	(-1.17)
Cell therapy	-0.004	0.035	-0.311**	-0.121***
	(-0.13)	(1.04)	(-2.52)	(-4.23)
Gene therapy	-0.047	-0.080**	-0.101	0.001
	(-1.31)	(-2.52)	(-1.02)	(0.04)
RNA	-0.095	0.018	-0.408**	-0.103*
	(-1.49)	(0.24)	(-2.13)	(-1.77)
Peptide	-0.129*	-0.075	0.138	-0.029
	(-1.72)	(-1.03)	(0.66)	(-0.44)
Fusion protein	0.062	-0.027	-0.093	-0.056
	(1.20)	(-0.57)	(-0.69)	(-1.14)
N	13847	16484	5117	17431

t statistics in parentheses. * $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$, all regressions contain fixed-effects for years, indications, and sponsors.

We see a consistent and negative impact on small molecule drugs: the probabilities for successful phase transitions and for LoA are lower in the EU after 2004, compared to Japan and the US. The size of the effect is 2-4 percentage points in Phase 1, Phase 2, and LoA, and almost 9 percentage points in Phase 3.

For cell therapies and RNA drugs, we observe lower success rates for Phase 3 and LoA. Gene therapies have a lower Phase 2 transition probability and peptide drugs a lower Phase 1 transition probability. As the estimated coefficients are based on very few observations (except for those on small molecule drugs), the size of the coefficients should be regarded as indicative at best. For example, the estimate that the Phase 3 transition probability of RNA based drugs has decreased by 40.8 percentage points is based on only 6 RNA based drugs developed in the EU after 2004. For antibody drugs, peptide drugs, and fusion proteins, we see no significant effects.

Thus, we find that the success of small molecule drugs in the EU has declined through all phases of clinical testing after 2004, relative to the US and Japan.

Analysis using propensity score matching

In the analysis so far, we have relied on using all available data on clinical trials in the EU, the US, and Japan. While this approach yields the most general results as all available data are used, there might also be drawbacks: if the composition of clinical trials differs across geographies, differences found between geographies might actually be due to differences in sample composition. To be specific, assume that the EU and the US are identical when it comes to regulatory and research conditions. If clinical trials in the EU systematically focus on therapeutic areas where progress is harder to achieve (relative to the trials conducted in the US), we would expect to see a lower rate of phase progressions in the EU. However, this lower rate would not be due to policy or regulation, but simply due to the fact that more challenging projects are attempted.

In this section, we will control for the composition of clinical trials across geographies through propensity score matching. Intuitively, we will i) estimate if clinical trials in the EU are statistically different from those in other regions based on their observable characteristics; ii) select for each EU trial a US or Japanese trial that is as similar as possible; and iii) repeat the above analysis in the resulting matched sample. By pairing EU and non-EU trials that are individually as similar as possible, we should obtain a sample that is on aggregate not too different across regions, based on the observable characteristics of drug trials.

The first step in this procedure is to estimate a selection model, in which the probability of a trial being conducted in the EU is estimated as a function of observable characteristics. Since the dependent variable is binary (EU 0/1), we estimate a probit model. The independent variables available refer to trial sponsors, an indicator for whether a trial is run for a combinatorial drug treatment, therapeutic area indications, and the phase of the trial. Estimation results are reported in the table below.

Table RI-6.4. Selection model: characteristics of European trials

Other pharma	-0.145***	(0.021)
Government	-0.410***	(0.019)
Top 20 pharma	-0.078***	(0.021)
Academic	-0.055***	(0.018)
Combinatorial drug	0.070***	(0.016)
Metabolic	0.209***	(0.026)
Cardiovascular	0.239***	(0.028)
CNS	0.184***	(0.022)
Autoimmune	0.349***	(0.022)
Genitourinary	0.334***	(0.043)
Infectious disease	0.299***	(0.023)
Ophthalmology	-0.027	(0.051)
Vaccines	0.638***	(0.035)
Phase 2	0.103***	(0.016)
Phase 3	0.297***	(0.019)
Observations	38501	
Pseudo R^2	0.030	

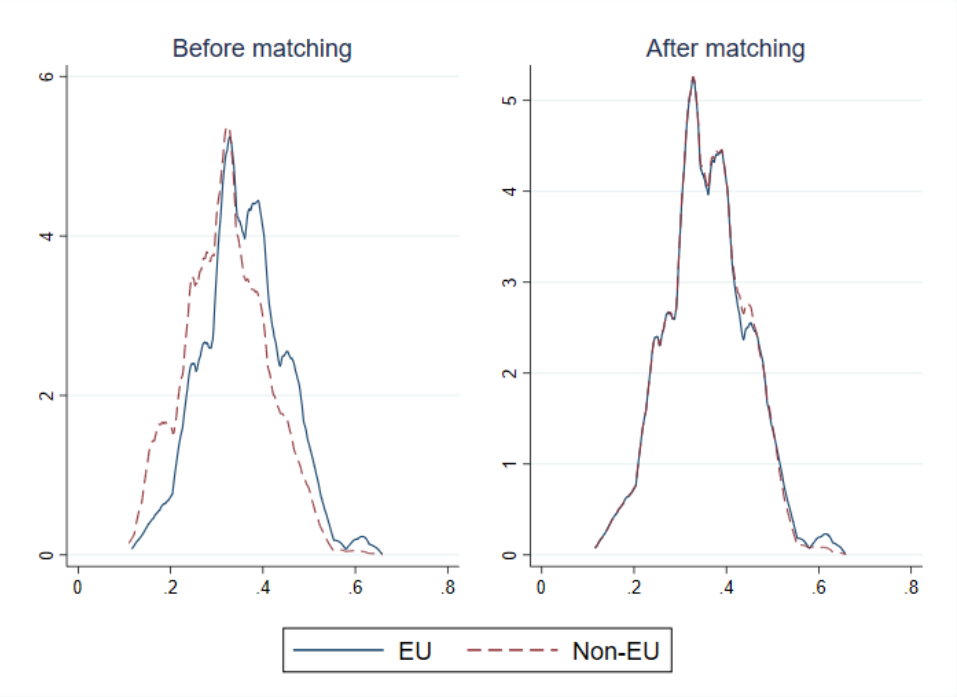
Standard errors in parentheses, * p < 0.1, ** p < 0.05, *** p < 0.01

The estimation results show that, on the one hand, European trials differ from US and Japanese trials in almost all observable characteristics, but – on the other hand – the amount of heterogeneity that can be explained through the observables is limited, as the explanatory power (the pseudo R^2) of the model is quite low.

European trials have, on average, fewer sponsors than those in other regions: the involvement of Top 20 pharma firms, other pharma firms, and academic participants is lower, and particularly government involvement is much lower than in the other regions. Combinatorial drugs are more likely to be tested in the EU. The probability of trials occurring in a specific therapeutic area are measured relative to the first therapeutic area in the data (oncology). The mostly positive and significant coefficients therefore suggest that the EU conducts relatively less trials in oncology compared to the US and Japan, but relatively more in most other therapy areas. Finally, we observe more Phase 2 and Phase 3 trials in the EU (compared to Phase 1 trials).

Thus, EU and non-EU trials are somewhat different with regard to their composition. To account for this, we implement a propensity score matching procedure as follows: first, we use the selection model calibrated above to obtain the predicted values. Thus, for every trial, we estimate the likelihood that this trial was conducted in the EU, based on the model coefficients. Next, for each European trial, we find a non-European trial (conducted in the same year) that is as similar as possible in its probability of being run

in Europe (i.e., with a very similar predicted value). By pairing EU and non-EU trials that are as similar as possible, we obtain a sample of (the same amount of) EU and non-EU trials with similar characteristics. Additional non-EU trials are discarded. The figure below plots the kernel densities of the propensity scores (i.e., the ex-ante likelihoods of being an EU trial) for EU and non-EU trials before (left) and after (right) the matching procedure. While the distribution of propensity scores across the two groups looks quite dissimilar in the left panel, the matching procedure results in almost identical kernel densities across the two groups. This shows that the samples have been made more comparable.



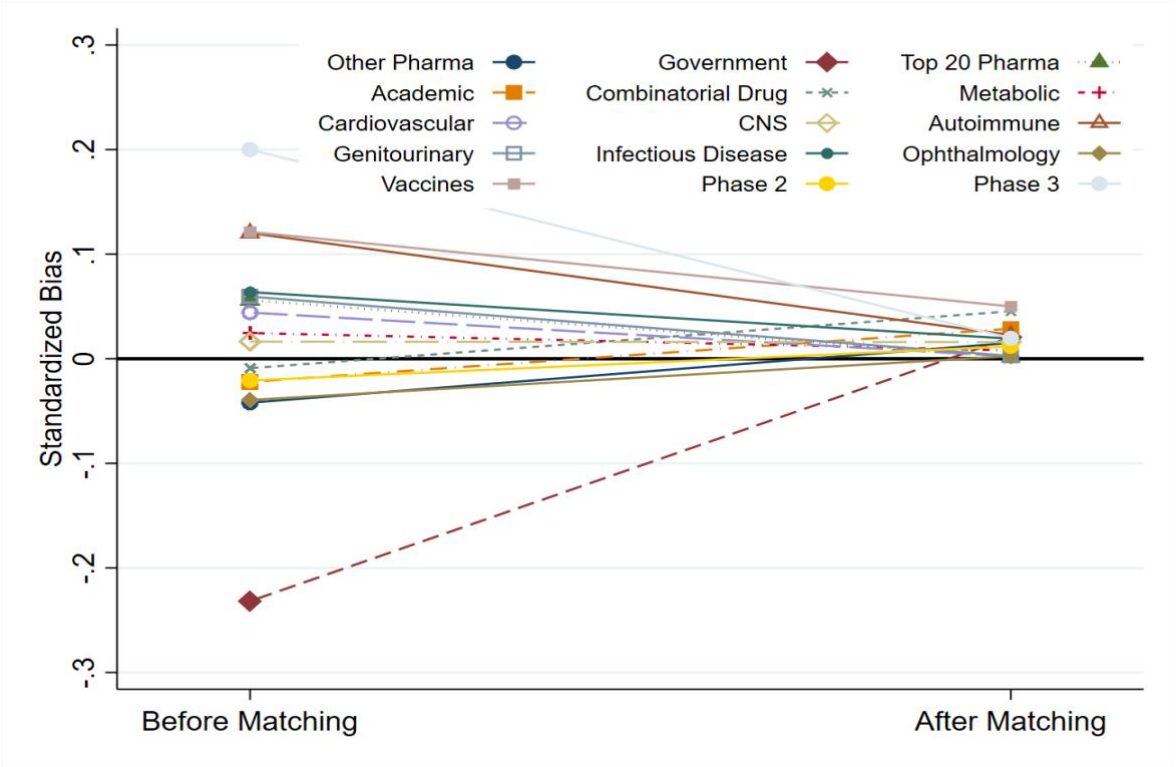
This can also be illustrated based on the trials' observable characteristics. The table below reports sample averages for all trial characteristics used in the matching procedure (sponsors, combinatorial drugs, therapeutic areas, and trial phases), distinguishing EU and non-EU trials and calculating the statistical significance of the difference between the two ("p"). Before the matching procedure (columns 1-3), almost all the means are significantly different between the two groups (as indicated by p-values smaller than 0.1 in column 3). Conversely, after the matching procedure, (columns 4-6), the means have become more similar and most differences now lack statistical significance, although some differences remain.

Table RI-6.5. Trial characteristics before and after matching

	Before matching			After matching		
	Mean EU	Mean non-EU	p	Mean EU	Mean non-EU	p
Other pharma	0.303	0.322	0.00	0.303	0.310	0.22
Government	0.127	0.213	0.00	0.127	0.120	0.10
Top 20 pharma	0.277	0.252	0.00	0.277	0.276	0.91
Academic	0.419	0.430	0.04	0.419	0.405	0.02
Combinatorial Drug	0.434	0.438	0.41	0.434	0.411	0.00
Metabolic	0.095	0.088	0.02	0.095	0.097	0.52
Cardiovascular	0.080	0.068	0.00	0.080	0.079	0.85
CNS	0.147	0.141	0.13	0.147	0.152	0.20
Autoimmune	0.154	0.113	0.00	0.154	0.163	0.07
Genitourinary	0.032	0.022	0.00	0.032	0.032	0.83
Infectious disease	0.134	0.113	0.00	0.134	0.127	0.12

Ophthalmology	0.016	0.021	0.00	0.016	0.016	0.84
Vaccines	0.055	0.030	0.00	0.055	0.044	0.00
Phase 2	0.421	0.432	0.06	0.421	0.427	0.34
Phase 3	0.268	0.184	0.00	0.268	0.259	0.12

Finally, the matching procedure can also be illustrated by comparing the standardized biases. The standardized bias (the difference in means of treatment and control group divided by the standard deviation in the treatment group) is the bias one incurs by comparing EU to non-EU trials. The figure below illustrates how standardized biases with regard to the individual matching variables change from before matching (left) to after matching (right). Most standardized biases are substantially reduced through matching; in particular, some heavily biased characteristics such as Phase 3 trials and government sponsors are much improved.



In the following, we repeat the regression analyses for indicators RI-2, RI-3, RI-4, and RI-6 in the propensity-score matched sample.

RI-2: Transition success rate (%) of candidates from Phase 1 to Phase 2 clinical trials

The table below compares the success rate of Phase 1 trials in the EU in the period including and after 2005 to the success rate before 2005, as well as to success rates in the US and Japan. Conducting the same analysis in the full sample, we found that success rates in the EU declined by 4-5%, significant at the 5-10% level. Estimating yearly ATEs, we found that all coefficients were negative, but only some were significant.

Repeating the analysis in the matched sample, we find no significant difference between Phase 1 success in the EU and the other regions after 2004. The coefficient estimates of the ATE are close to zero and not statistically significant, both including year fixed-effects (column (1)) and including year and indication fixed-effects (column (2)). When looking at yearly ATEs in column (3), we see that the coefficients are never significantly different from zero.

Table RI-2: transition success rate (%) of candidates from Phase 1 to Phase 2 clinical trials in matched sample

	(1)		(2)		(3)	
ATE	0.014	(0.51)	0.010	(0.39)		
2005					0.035	(0.65)
2006					0.016	(0.29)
2007					0.002	(0.03)
2008					-0.036	(-0.82)
2009					0.004	(0.08)
2010					0.027	(0.62)
2011					0.012	(0.26)
2012					0.050	(1.11)
2013					0.000	(0.01)
2014					0.017	(0.40)
2015					0.019	(0.43)
2016					-0.017	(-0.37)
2017					0.025	(0.57)
2018					-0.067	(-1.47)
2019					0.030	(0.61)
2020					0.030	(0.68)
N	8019		8019		8019	

t statistics in parentheses. Column (1) contains fixed-effects for years and sponsor types; column (2) adds fixed-effects for indications. Column (3) estimates separate treatment effects for each post-period. * $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

Thus we conclude that once we control for differences in the observable characteristics of clinical trials across regions, there are no significant differences in successful Phase 1 trials in the EU vis-à-vis the other regions after 2004.

RI-3: Transition success rate (%) of candidates from Phase 2 to Phase 3 clinical trials

Next, we analyse the impact on RI-3 in the matched sample. Recall that above we found successful Phase 2 trials had become about 4% less likely in the EU after 2004.

The table below reports the findings from the matched sample. While the two estimates of the ATE in columns (1) and (2) remain negative, they lose their statistical significance. The year-specific ATEs (column (3)) reveal that the effect is significant only in one period, 2009. While some indications of a negative impact on Phase 2 trial success remain, the treatment effects are mostly insignificant in the matched sample.

Table RI-3: transition success rate (%) of candidates from Phase 2 to Phase 3 clinical trials in matched sample

	(1)		(2)		(3)	
ATE	-0.011	(-0.69)	-0.013	(-0.83)		
2005					-0.038	(-1.18)
2006					0.003	(0.08)
2007					0.015	(0.47)
2008					0.023	(0.70)
2009					-0.079***	(-2.64)
2010					0.004	(0.13)
2011					-0.008	(-0.23)
2012					0.002	(0.07)
2013					-0.033	(-1.00)
2014					0.007	(0.21)
2015					-0.029	(-0.84)
2016					-0.020	(-0.61)
2017					-0.020	(-0.59)
2018					0.012	(0.33)
2019					-0.015	(-0.42)
2020					-0.011	(-0.36)

N	10870		10870		10870	

t statistics in parentheses. Column (1) contains fixed-effects for years and sponsor types; column (2) adds fixed-effects for indications. Column (3) estimates separate treatment effects for each post-period. * p < 0.1, ** p < 0.05, *** p < 0.01

Thus, there are only minor differences in successful Phase 2 trials in the EU vis-à-vis the other regions after 2004.

RI-4: transition success rate (%) of candidates from Phase 3 to approval

The next indicator we re-evaluate in the matched sample is the rate of successfully completed Phase 3 trials (Phase 3 to approval). In the full sample above, we found that although the ATE coefficients were negative, EU Phase 3 trials were not significantly less successful than those in other regions.

This finding is replicated for the matched sample in the table below. The ATE coefficients are very similar to those obtained in the full sample and not statistically significant. The estimated yearly effects are also insignificant, except for two periods, where marginal significance is attained.

Table RI-4: transition success rate (%) of candidates from Phase 3 to approval in matched sample

	(1)		(2)		(3)	
ATE	-0.035	(-1.10)	-0.034	(-1.09)		
2005					0.041	(0.60)
2006					-0.079	(-1.21)
2007					0.065	(0.91)
2008					0.003	(0.04)
2009					-0.062	(-0.88)
2010					0.036	(0.52)
2011					-0.117*	(-1.68)
2012					-0.039	(-0.53)
2013					-0.080	(-1.05)
2014					-0.062	(-0.80)
2015					-0.030	(-0.38)
2016					0.092	(1.10)
2017					-0.064	(-0.76)
2018					-0.042	(-0.47)
2019					-0.074	(-0.87)
2020					-0.152**	(-2.08)
N	4151		4151		4151	

t statistics in parentheses. Column (1) contains fixed-effects for years and sponsor types; column (2) adds fixed-effects for indications. Column (3) estimates separate treatment effects for each post-period. * p < 0.1, ** p < 0.05, *** p < 0.01

Thus, the success rate of Phase 3 trials in the EU after 2004 did not differ substantially from that in the other regions.

RI-6: Overall likelihood of approval from Phase 1

Next, we turn to the overall likelihood of approval for drugs. In the full sample, we found i) no significant overall impact in the EU after 2004 and ii) positive as well as negative effects in some specific years.

In the matched sample we find – as reported in the table below – no significant differences between the EU and the other regions, neither in the overall ATEs, nor in the disaggregated yearly coefficients.

Table RI-6.1: overall likelihood of approval from Phase 1 in matched sample

	(1)		(2)		(3)	
ATE	0.012	(0.69)	0.010	(0.59)		
2005					0.014	(0.40)
2006					0.004	(0.12)
2007					0.018	(0.50)
2008					0.008	(0.24)
2009					0.019	(0.57)
2010					0.041	(1.23)
2011					-0.033	(-1.00)
2012					0.015	(0.42)
2013					-0.010	(-0.30)
2014					0.016	(0.46)
2015					0.012	(0.34)
2016					0.048	(1.41)
2017					0.005	(0.16)
2018					-0.007	(-0.19)
2019					-0.001	(-0.03)
2020					-0.017	(-0.54)
N	12407		12407		12407	

t statistics in parentheses. Column (1) contains fixed-effects for years and sponsor types; column (2) adds fixed-effects for indications. Column (3) estimates separate treatment effects for each post-period. * $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

Thus, the overall likelihood of drug approval did not change in the EU after 2004.

Heterogeneous effects in the PSM sample

For completeness and to corroborate the previous findings, we also repeat the analyses of heterogeneous effects (specifically, the impact of therapeutic area, of trial sponsor, and of drug modality on the indicators) in the propensity score matched sample.

Therapy areas

In the full sample it was found that in some therapeutic areas (CNS, autoimmune, infectious disease) the EU seems to be at a disadvantage, particularly in earlier trial phases.

On the one hand, these findings of a negative effect are largely replicated in the matched-sample analysis below. Specifically, we see that Phase 2 success is lower for autoimmune and infectious disease drug trials, and Phase 3 success is lower for autoimmune disease drug trials.

On the other hand, we also find positive effects on trial success in the matched sample. The Phase 3 and LoA success of oncology drugs has increased by 11 and 9 percentage points respectively, and the Phase 1 and LoA success for vaccines trials in the EU has increased by 8 percentage points. For the other therapeutic areas, no significant effects are found.

Table RI-6.2 Phase transitions and LoA by therapeutic area in matched sample

	(1) Phase 1	(2) Phase 2	(3) Phase 3	(4) LoA
Oncology	-0.030	0.029	0.113**	0.086***
	(-0.99)	(1.56)	(2.01)	(3.80)
Metabolic	-0.002	0.005	-0.021	-0.018
	(-0.06)	(0.20)	(-0.42)	(-0.72)
Cardiovascular	0.025	-0.043	-0.076	-0.022

	(0.58)	(-1.47)	(-1.46)	(-0.78)
CNS	-0.003	-0.031	-0.075	-0.020
	(-0.09)	(-1.42)	(-1.63)	(-0.88)
Autoimmune	0.030	-0.038*	-0.073*	-0.008
	(0.89)	(-1.77)	(-1.66)	(-0.35)
Genitourinary	0.071	-0.038	-0.015	-0.053
	(1.04)	(-0.89)	(-0.20)	(-1.33)
Infectious disease	0.042	-0.047**	-0.078	0.001
	(1.19)	(-1.97)	(-1.63)	(0.03)
Ophthalmology	-0.039	0.034	0.025	0.047
	(-0.48)	(0.62)	(0.26)	(0.99)
Vaccines	0.076*	-0.040	0.130	0.081**
	(1.87)	(-1.05)	(1.62)	(2.26)
N	8019	10870	4151	12407

t statistics in parentheses. * p < 0.1, ** p < 0.05, *** p < 0.01, all regressions contain fixed-effects for years, indications, and sponsors.

Thus, the finding that some (Phase 2 and 3) success rates have decreased in the EU is corroborated in the matched sample. Yet, we additionally find that the overall likelihood of approval rate has increased for oncological drugs and vaccines.

Trial sponsors

Second, we estimate heterogeneous effects for trial sponsor types (top 20 pharma, other pharma, government, and academic) in the matched sample. In the full sample, it was found for the EU that academic-backed trials have a lower Phase 3 success rate; that top 20 pharma firm trials have a higher Phase 3 success rate, but lower Phase 1, Phase 2, and LoA success rates; that government-backed trials are highly successful in Phase 3 and LoA; and that other pharma firms are at a disadvantage in Phase 1 and Phase 2 trials.

Most of these findings are corroborated in the table below. While the negative impact on top 20 pharma firms' LoA and the effects on other pharma firms have vanished, the coefficients for academic- and government-backed trials are very similar to above.

Table RI-6.3 Phase transitions and LoA by trial sponsor in matched sample

	(1) Phase 1	(2) Phase 2	(3) Phase 3	(4) LoA
Academic	-0.005	0.004	-0.081**	-0.008
	(-0.21)	(0.33)	(-2.42)	(-0.47)
Top 20 pharma	-0.023	-0.060***	0.070*	-0.016
	(-0.99)	(-3.40)	(1.89)	(-0.90)
Government	0.006	0.006	0.115**	0.099***
	(0.21)	(0.29)	(1.97)	(4.22)
Other pharma	-0.009	-0.021	-0.035	0.016
	(-0.41)	(-1.36)	(-1.04)	(1.03)
N	8019	10870	4151	12407

t statistics in parentheses. * p < 0.1, ** p < 0.05, *** p < 0.01, all regressions contain fixed-effects for years, indications, and sponsors.

Thus, the finding that after 2005 in the EU government-backed trials were particularly successful in the later stages of testing is reinforced.

Drug modality

Finally, we estimate heterogeneous effects for drug modalities. In the full sample, it was found that small molecule drugs in the EU have lower chances of being successfully tested in all phases of testing, including LoA. While negative effects were also found in some other modality groups, those were estimated based on few observations and have to be interpreted with caution.

The results in the matched sample, by and large, mirror those found in the full sample. While the negative effects of small molecule drugs are insignificant in Phases 1 and 2 in the matched sample, the negative effects on Phase 3 and LoA retain statistical significance.

Table RI-6.4 Phase transitions and LoA by drug modality

	(1) Phase 1	(2) Phase 2	(3) Phase 3	(4) LoA
Small molecule	-0.022	-0.003	-0.092***	-0.023*
	(-1.32)	(-0.27)	(-3.30)	(-1.73)
Antibody	0.043*	0.009	0.048	-0.005
	(1.82)	(0.54)	(0.83)	(-0.22)
Cell therapy	0.002	0.047	-0.317**	-0.120***
	(0.06)	(1.33)	(-2.57)	(-3.93)
Gene therapy	-0.041	-0.072**	-0.100	0.011
	(-1.13)	(-2.19)	(-1.02)	(0.33)
RNA	-0.091	0.040	-0.390**	-0.090
	(-1.39)	(0.50)	(-2.05)	(-1.46)
Peptide	-0.120	-0.067	0.160	-0.028
	(-1.56)	(-0.89)	(0.76)	(-0.41)
Fusion protein	0.069	-0.018	-0.092	-0.064
	(1.30)	(-0.36)	(-0.68)	(-1.19)
N	8019	10870	4151	12407

t statistics in parentheses. * $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$, all regressions contain fixed-effects for years, indications, and sponsors.

Thus, the finding that after 2005 in the EU small molecule trials were less successful in the later stages of testing is reinforced.

Summary

The analyses of clinical trial data, and, specifically, the probabilities of successfully completing Phase 1, Phase 2, and Phase 3 trials, as well as successfully reaching marketing approval, have yielded mixed results. No clear-cut and robust divergence of success in clinical testing between the EU and the US/Japan has been found in the 2005-2020 period. This is not too surprising, as the "treatment" being evaluated in the analysis (the change of pharmaceutical regulations in the EU that came into force in 2005) did not occur randomly or in isolation. Also, rather than comparing a specific policy in one region to regions without that policy, we are evaluating the impact of a large set of regulations relative to a moving benchmark. This makes it difficult to identify any causal effect of such a treatment, particularly over such a long period of observation. The tendencies uncovered in the above analysis should therefore be regarded as the result of the entire research environment in the EU, including pharmaceutical regulations, but also other factors such as the availability of research funding and technological opportunities.

Methodologically, we analysed both the full dataset available and a propensity-score

matched sample, where for each EU trial we chose a non-EU trial that is as similar as possible in terms of observable characteristics. While the former approach covers the whole data range available, the latter approach controls for differences in, e.g., the composition of trials in the different regions. Thus, for the purposes of informing policy, the PSM approach is preferable and should be given more weight, as it makes sure that "apples are compared to apples".

While in the full sample, the likelihood of Phase 1 and Phase 2 success diminishes slightly in the EU vis-à-vis the other regions, these findings cannot be replicated in the matched sample. For successful Phase 3 trials and the overall likelihood of approval, findings are inconclusive in both evaluated samples. These results are summarized in the table below.

Table RI-6.5. Summary of findings on EU performance relative to US/Japan performance on main indicators

Indicator	Full sample	Matched sample
RI-2		
RI-3		
RI-4		
RI-6		

We do, on the other hand, find some interesting and robust patterns when looking at heterogeneous effects.

When differentiating trial success by therapeutic area, we find that the likelihood of successful Phase 2 trials has diminished in the EU for trials in five areas, two of which (autoimmune and infectious diseases) are corroborated by the matching analysis. For autoimmune diseases, Phase 3 trials are also less likely to be successful.

Looking at trial success by sponsor type, we find in the full sample analysis and corroborate in the matched sample analysis that Phase 2 trials by large pharmaceutical companies and Phase 3 trials by academic sponsors have become less likely to succeed in the EU in the period after 2004. Conversely, Phase 3 trials sponsored by large pharmaceutical companies, as well as Phase 3 trials and the likelihood of approval of drugs trialled in government-backed research have become more successful.

Finally, the analysis of heterogeneities by drug modalities has shown that Phase 3 trials have become less successful in the EU in the areas of small molecule drugs, cell therapies, and RNA drugs, and that the overall likelihood of approval has diminished for the former two.

RI-7: Number of grants and value of grant funding by country

Indicator definition and relevance with respect to the evaluation

Public R&D investment is an important indicator of the status of fundamental scientific research, as it is the ultimate source of much innovation in the pharmaceutical industry.

While no data are available for the analysis period prior to the introduction of the general pharmaceutical legislation, RI-7 assesses the relative investment in fundamental scientific research by certain member states of the EU between 2015 and 2020, where the most complete data are available.

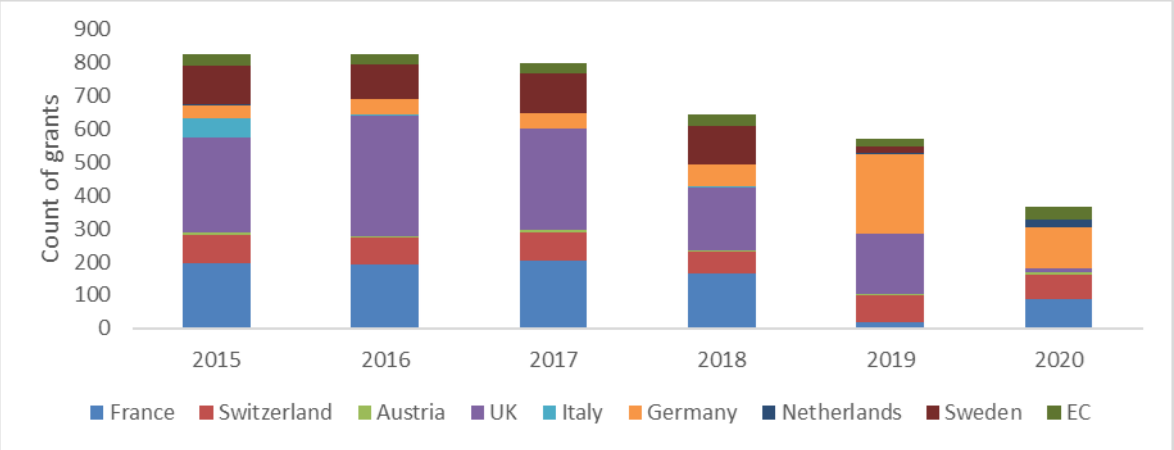
Methodology

The scientific grants analysis dataset for indicator RI-7 consists of approximately 6,500 grant records that have been collected and curated by Informa Pharma Custom Intelligence. When grants were extracted from a country or funding body database, they were screened to select only grants that might potentially lead to the development of a medicinal product, in order to prevent any analysis of the grants data from being confounded by grants not relevant to pharmaceutical innovation. Data were gathered from more than 20 grant agencies across 9 countries in the EU, plus the EC's H2020 and FP7 programmes, and Switzerland. The data available in each funding body database are not consistent, so temporal data for Spain are unavailable, and total or average grant values are not available for the Netherlands or Germany, so these data are not presented.

Description of trends and interpretation of possible causes for changes in RI-7

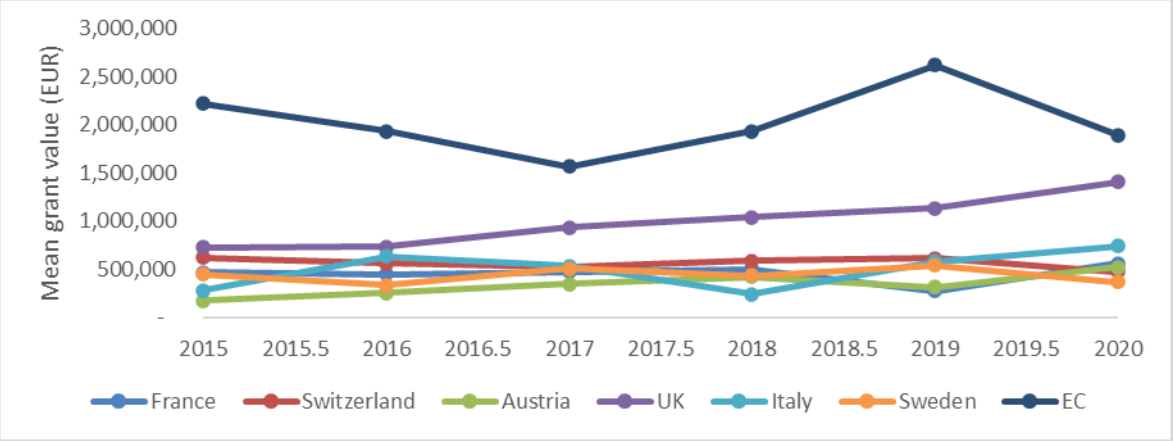
While no data for the period prior to the implementation of the general pharmaceutical legislation were available, the number of grants and the average value of grants over time are shown in Figure RI-7.1 and Figure RI-7.2, respectively. Only 6 years of complete data for 8 member states were available, plus data for the EC, but these data show that, in general, the overall number of grants is decreasing, while the average grant value stays relatively constant. This is in line with a known trend in the funding of fundamental scientific research, where in recent years decisions taken by funding bodies are often to award larger sums to fewer academic or research institutions or consortia of academic or research institutions with a lead institution (with or without industrial partnerships) that is responsible for allocating funding to smaller partners or projects in the consortium. This is generally seen as more efficient, as the main funding body has fewer applications to consider each year.

Figure RI-7.1 Total number of grants starting each year (2015-2020).



Source: Informa grants database (2015-2020).

Figure RI-7.2 Average value of grants starting each year (2015-2020).

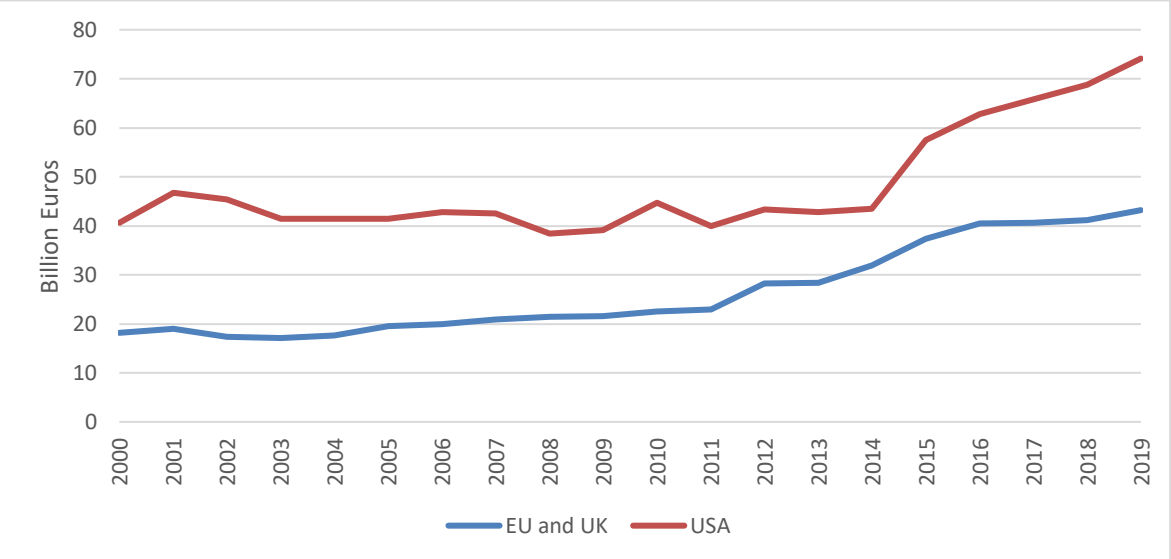


Source: Informa grants database (2015-2020).

RI-8: Amount of private R&D investment in the sector

There has been an increase in total R&D expenditure, as captured by the EU R&D Scoreboard, doubling from around €20bn in 2000 to more than €40bn in 2019, albeit there is no significant change in investment evident in data in the 3-5 year period around the implementation of the legislation. Indeed, the data show two distinct phases, with the first 10 years largely flat, with investment struggling to keep pace with inflation, and with a second phase, where investment levels have increased strongly. The highest and most persistent growth in R&D investment in EU companies that operate in pharmaceuticals and biotechnology took place in 2011-2016. This is in line with global trends, whereby the OECD review of research and development in the pharmaceutical sector (2019) concluded that expenditure on R&D in the pharmaceutical industry across the OECD grew by 14% in real terms, between 2010 and 2016. On the other hand, in the US, R&D investment remained almost stationary from 2003 until 2011 (close to €40bn) and experienced significant growth in the period between 2014 and 2019.

Figure RI-8: Private R&D investment in pharmaceuticals and biotechnology in the EU and UK relative to the US



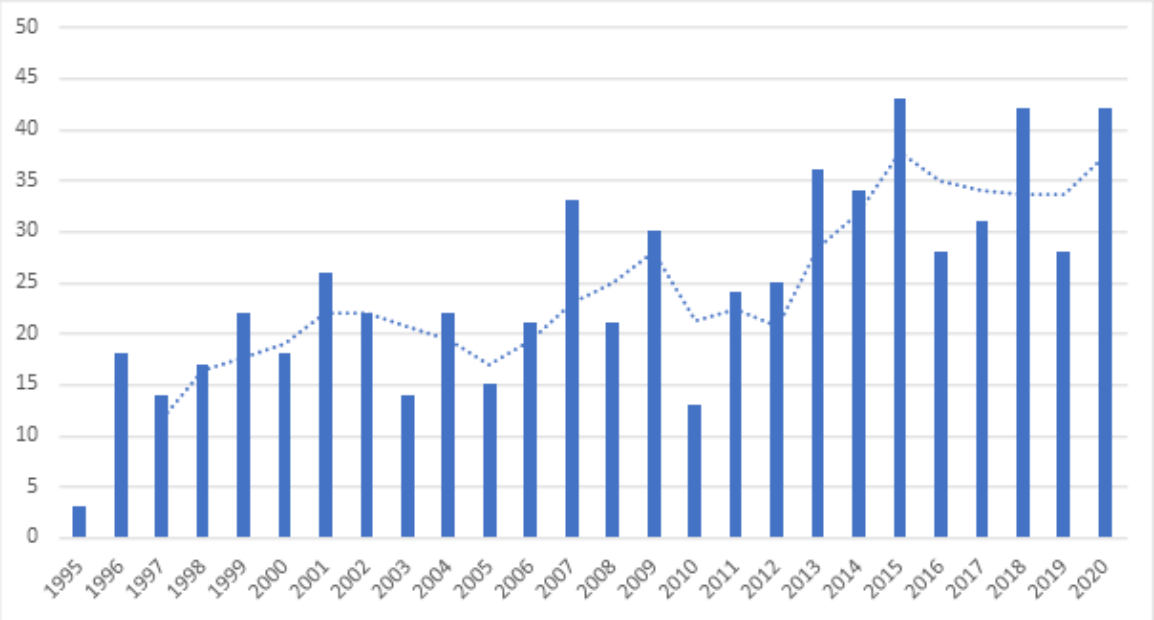
Source: EU Industrial R&D Investment Scoreboard (2000-2019). The figure shows annual R&D investment of the top EU+UK companies operating in the pharmaceuticals and biotechnology sector. Data for 2000-2003 is based on TOP500 companies; data for 2004 is based on TOP700 companies. From 2005 onwards, data is based on TOP1000 companies. Data for the US comes from Congressional Budget Office's April 2021 report Research and Development in the Pharmaceutical Industry.

RI-9: Number of innovative medicines

To provide insight in the yearly number of innovative medicines authorised by EMA we developed two definitions of 'innovative medicines'.

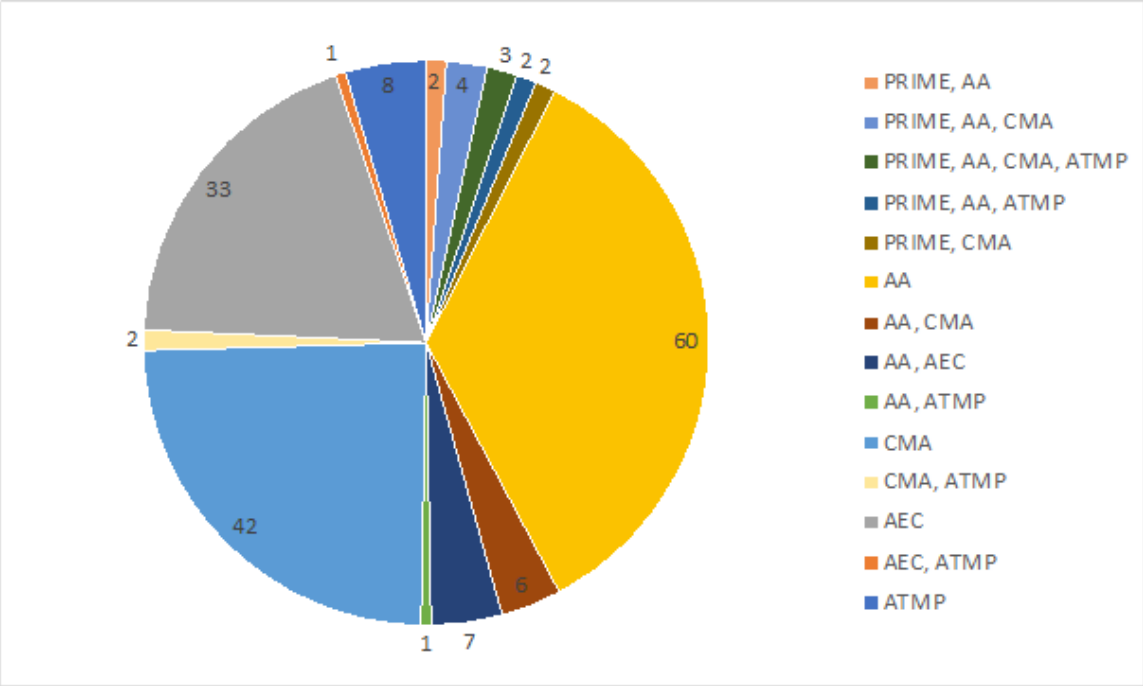
1. New active substances centrally (NAS) authorised by EMA. As medicinal products are only qualified as new active substances by the CHMP since 2011 we use this NAS qualification after 2011 and apply a similar methodology to classify medicines as NAS before 2011. Moreover, in case of multiple applications for the same substance including applications as combination medicines we remove duplicates and use the first date the active substance was authorised. A comparison of NASs with NMEs approved at FDA is provided in ACC-1.
2. All medicines that address unmet medical needs and/or are innovative from a technological point of view. This definition includes all medicines designated a PRIority MEdicine (PRIME), all medicines authorised under exceptional circumstances (AEC) or via the conditional marketing authorisation (CMA) pathway, all medicines for which Accelerated Assessment (AA) was granted by the CHMP and all authorised Advanced Therapy Medicinal Products (ATMP). We show absolute numbers (Figure RI-9.2 and RI-9.3) as well as the proportion of innovative medicines relative to the total number of full applications (Figure RI-9.4). The data covers medicines regulated under Regulation 726/2004 (since 2006) given that most pathways used for this definition did not exist before implementation of Regulation 726/2004.

Figure RI-9.1: Number of new active substances authorised by EMA (yearly, 1995-2020) (definition 1)



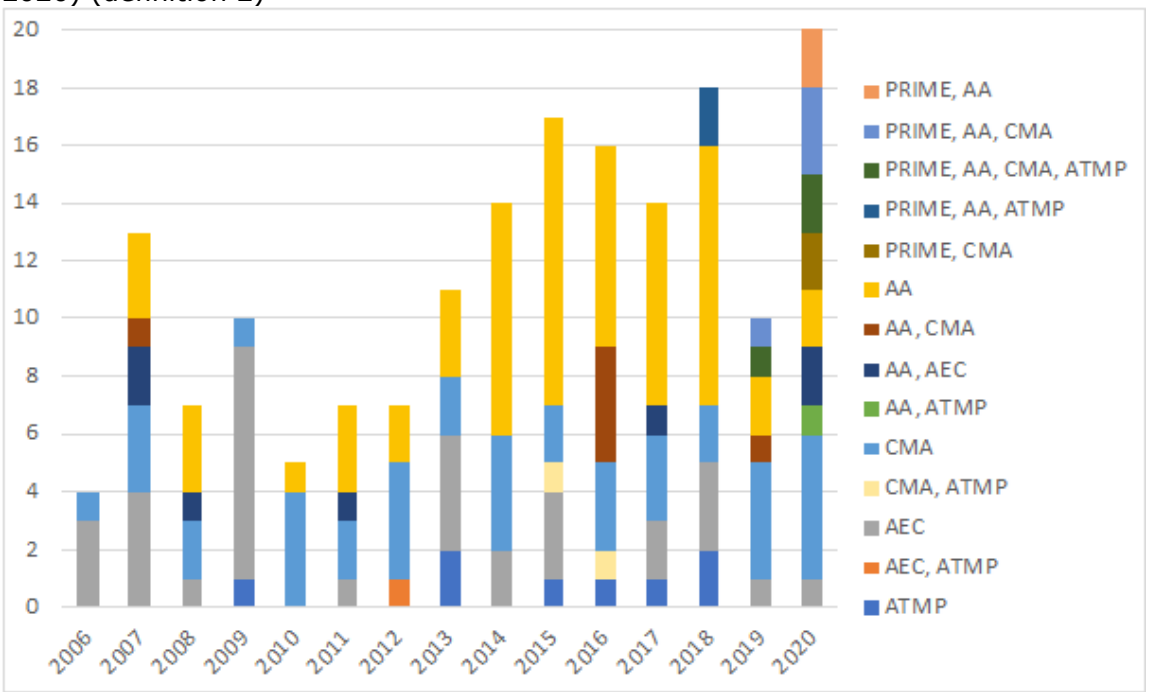
Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

Figure RI-9.2: Number of innovative medicines authorisations by EMA (overall, 2006-2020) (definition 2)



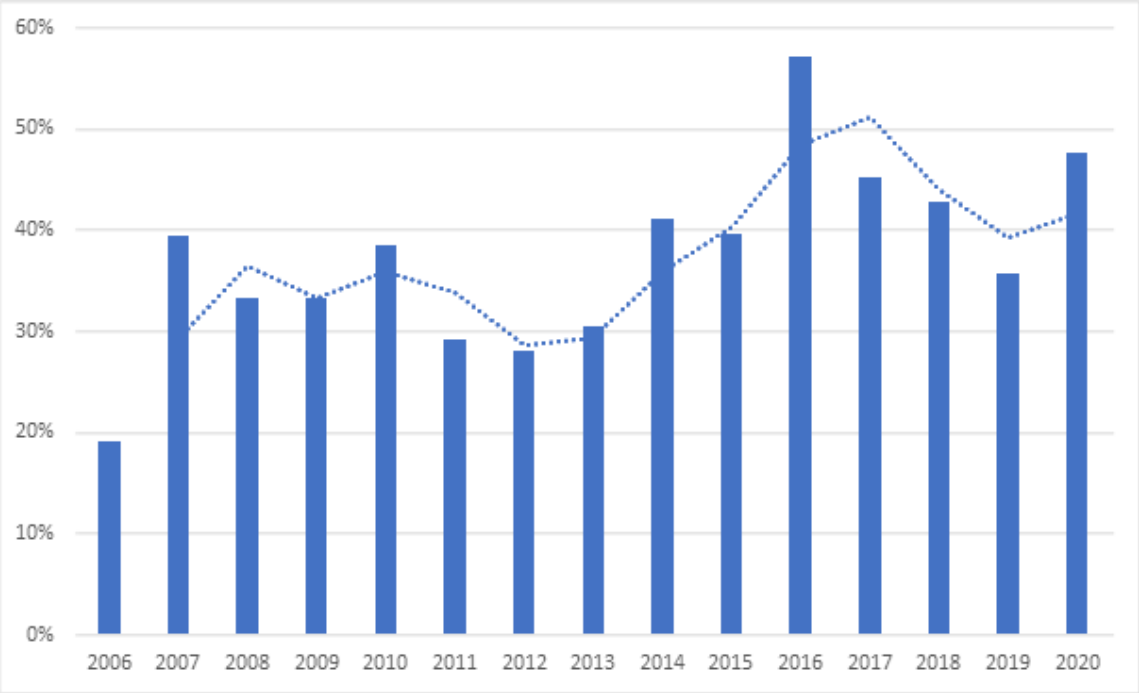
Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

Figure RI-9.3: Number of innovative medicines authorisations by EMA (yearly, 2006-2020) (definition 2)



ATMP = Advanced Therapy Medicinal Product; CMA = Conditional Marketing Autorisation; PRIME = Priority Medicine; AA = Accelerated Assessment granted; AEC = Authorisation under exceptional circumstances. Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

Figure RI-9.4: Proportion of innovative medicines authorisations (definition 2) relative to the total number of new active substances (definition 1), (yearly, 2006-2020)



Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

The number of innovative drugs gradually increases over time, particularly from 2012 onwards and when looking at products that address unmet medical needs and/or are innovative from a technological point of view.

The increase is also visible when looking at drugs that address an unmet medical need as a proportion of the total number of new active substances.

Over time, there is also an increase in the combined use of pathways – especially those including PRIME (in 2020).

1.3 ACCESS INDICATORS

Indicator name	Indicator description
	Access to approved medicines:
ACC-1	Number of medicines authorised
ACC-2	Speed of approval for authorised medicines
ACC-3	Number of approved medicines with zero sales volume in EU countries*
	Time to coverage:
ACC-4	Time from authorisation to non-zero sales volume reported for authorised medicines in individual EU countries*
ACC-5	Share of EU population with access to medicines sold on the market*
ACC-6	Number of lead and co-lead assessments by national regulatory authorities (rapporteurs and co-rapporteurs)
ACC-7	Number of indication extensions after first authorisation*
ACC-8	Number of market withdrawals
ACC-9	Time from market authorisation to market withdrawal
ACC-10	Number of Type I and Type II variations

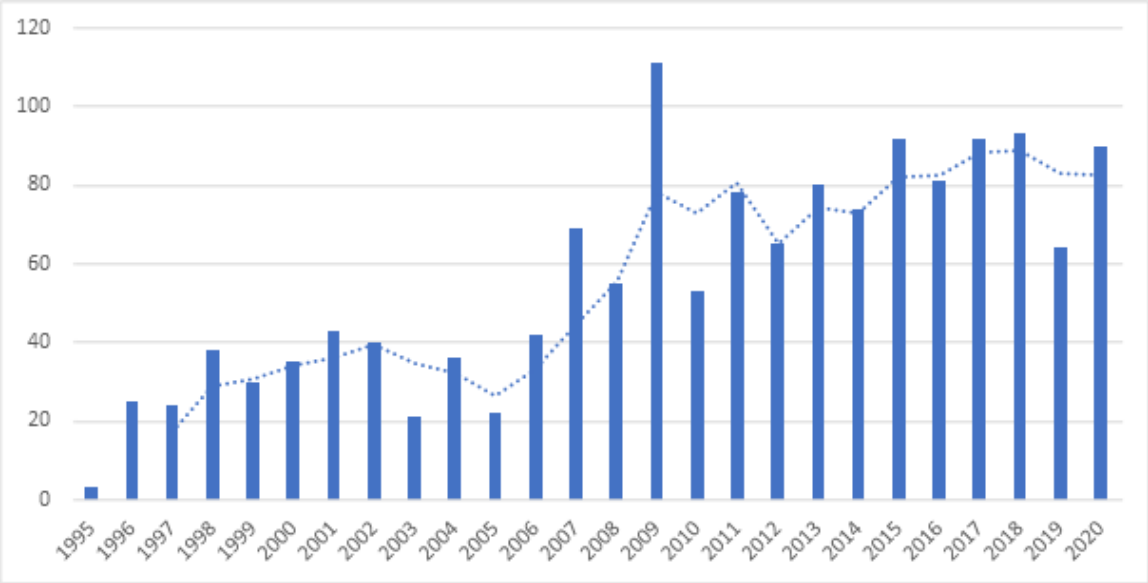
* Note that these indicators were not calculated

ACC-1: Number of medicines authorised

Figure ACC-1.1 provides an overview of the total number of medicinal products that were granted a market authorisation under the centralised authorisation by EMA per year (1995-2020). This includes all centrally authorised medicinal products authorised under Regulation 2309/93 (n = 317) and under Regulation 726/2004 (n = 1,139), irrespective of their legal basis (see indicator EFF-2 for a stratification by legal basis).
Figure ACC-1.2. focuses specifically on new active substances (NASs) centrally authorised by EMA and compares the yearly number of authorisations with the approval of New Molecular Entities (NMEs) by the FDA. As medicinal products are only qualified as NASs by the CHMP since 2011, the database uses a similar definition to classify medicinal products as NAS before 2011. Moreover, in case of multiple applications for the same substance including applications as combination medicines we remove duplicates and use the first date on which the substance was authorised.

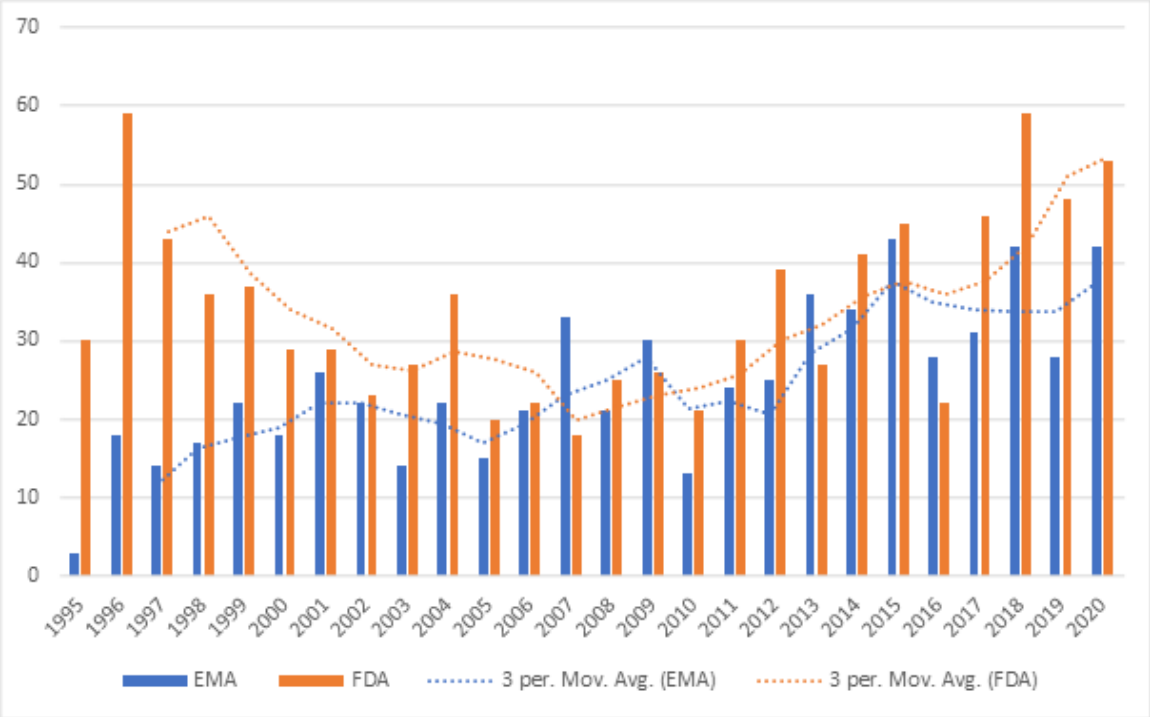
Figure ACC-1.3 and ACC-1.4 provides one-to-one comparisons between NASs/NMEs authorised by EMA/FDA to provide insight into whether the same NAS/NME is authorised earlier by EMA or FDA. When an active substance qualified as NAS/NME was authorised by EMA and FDA up to 31st December 2020 they were matched based on the following matching criteria: same brand name OR same applicant OR - if not same brand name or same applicant - same substance authorised within two years (earlier/later) of each other. Figure ACC-1.3 shows the time difference from the perspective of NASs authorised by EMA, i.e. the time difference in approval date with FDA of all NASs authorised by EMA. Figure ACC-1.4 the time difference in approval date of all new active substances/new molecular entities authorised by EMA and/or FDA (five-year periods, 1995-2020)

Figure ACC-1.1: Total number of centrally authorised medicinal products by EMA (yearly, 1995-2020)



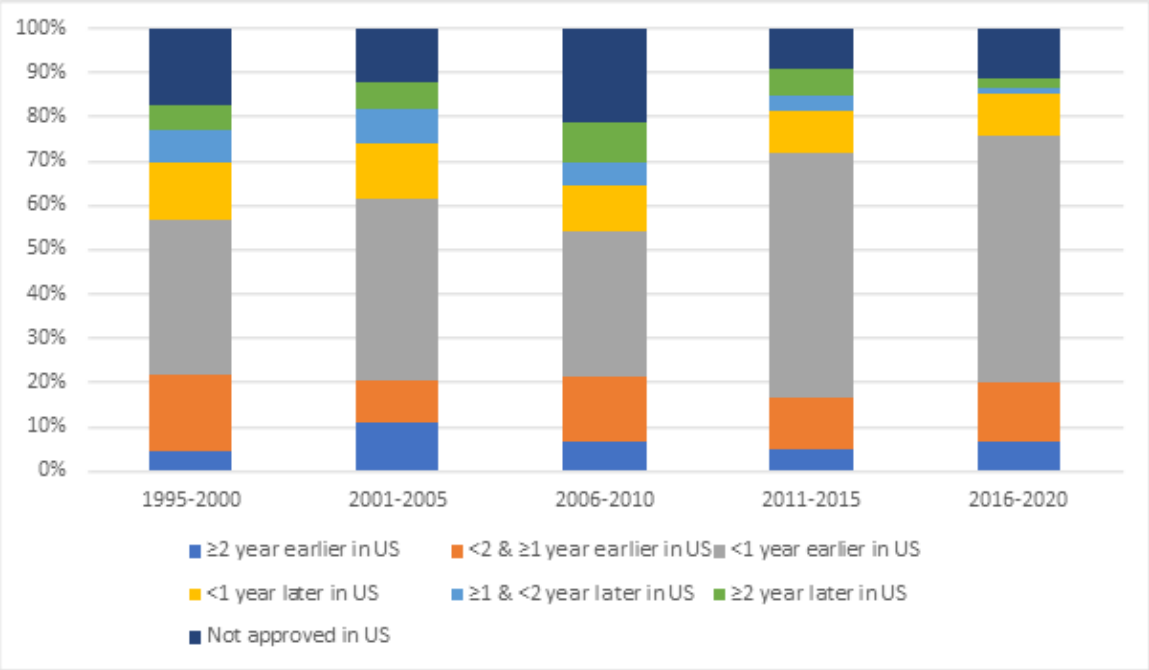
Note: trend-line indicates three-year moving average. Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

Figure ACC-1.2: Total number of new active substances/new molecular entities authorised by EMA and FDA (yearly, 1995-2020)



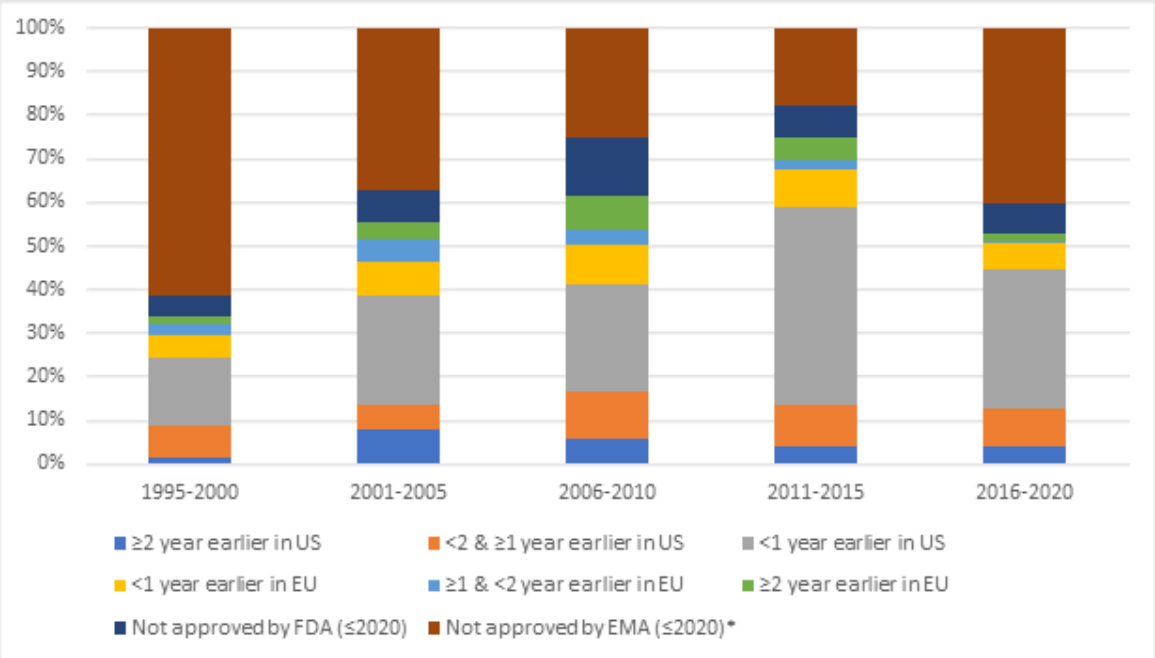
Note: trend-line indicates three-year moving average. Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

Figure ACC-1.3: Time difference in approval date with FDA of new active substances authorised by EMA (five-year periods, 1995-2020)



Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

Figure ACC-1.4: Time difference in approval date of all new active substances/new molecular entities authorised by EMA and/or FDA (five-year periods, 1995-2020)



* Some of the new molecular entities in this category might be authorised through the decentralised or mutual recognition procedure or authorised after 2020. Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

It was found that:

- Figure ACC-1.1 shows an increase in the number of medicinal products authorised through EMA's centralised procedure over time, stabilising somewhat around the mid-2010s
- A steep increase in the three-year moving average is particularly visible in the period 2005-2009 possibly following from the widening of the mandatory scope

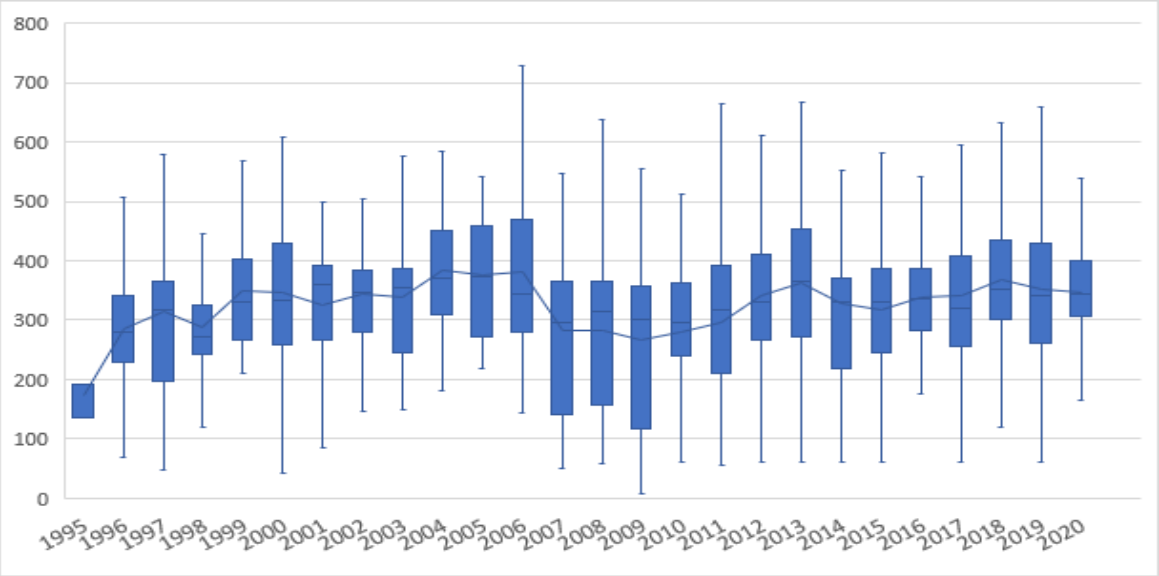
of the centralised procedure in Regulation (EC) No 726/2004, see also Figure EFF-2-1 for a stratification by legal basis
- Figure ACC-1.2 shows a gradual increase in the number of new active substances authorised through EMA's centralised procedure over time
- The 3-year moving average of the number of FDA authorised new molecular entities decreases up to 2007 and gradually starts to increase afterwards
- The number of FDA authorised new molecular entities is higher than the number of EMA authorised new active substances in almost every year in the period 1995-2020. In 2016-2020 we observe 171 new active substances authorised by EMA and 228 new molecular entities by the FDA.
- Figure ACC-1.3 and ACC-1.4 show that the majority of new active substances is authorised earlier by the FDA over the entire period
- Over time, the proportion of substances authorised <1 year earlier by the FDA than EMA is increasing. This group comprise the majority of substances (~55%) in the period 2011-2020.
- Over time, the proportion of FDA authorised substances not authorised by EMA decreases, with the exception of the latest period (2016-2020) which is probably due to censoring issues.

ACC-2: Speed of approval for authorised medicines

Figure ACC-2.1 shows the median and mean (line) total assessment time (in days) of all centrally authorised medicinal products per year. Total assessment time in days comprises a combination of active assessment time by EMA and clock-stop time by the applicant. Assessment times exclude the time for the European Commission to authorise the CHMP opinion (maximum 67 additional days).

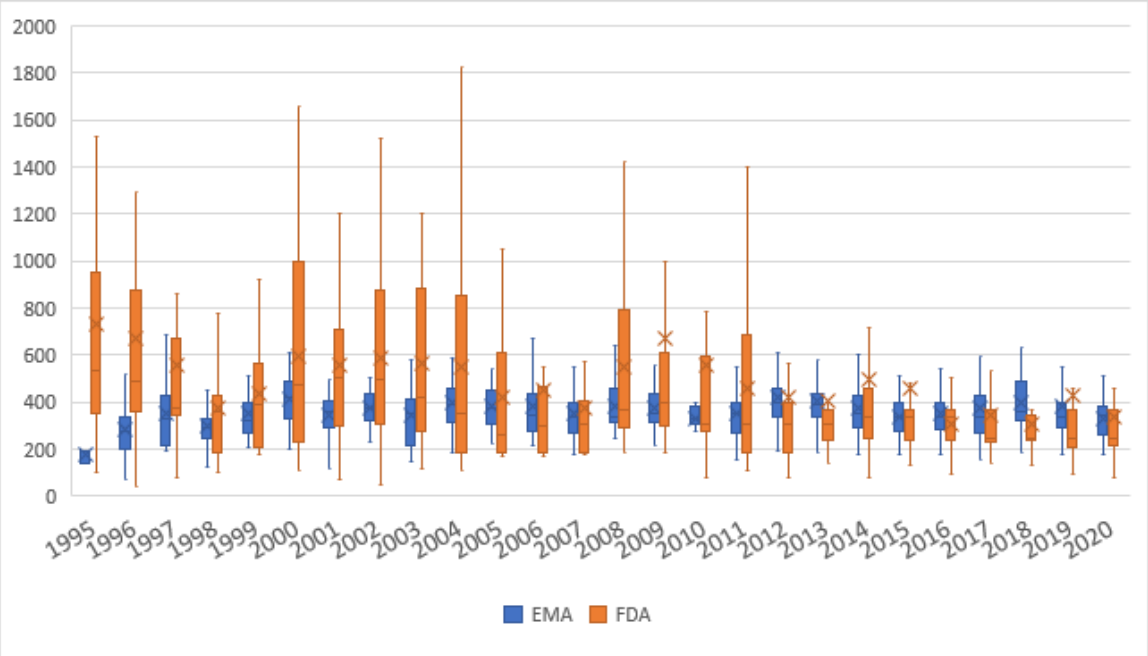
In Figure ACC-2.2 mean and median assessment times are visualized for NASs centrally authorised by EMA and compared to assessment times for NMEs by the FDA. Assessment times by FDA are calculated as the date the first and complete marketing application was received by FDA until the data the FDA authorised the original application. When comparing assessment times between jurisdictions it thus needs to be taken into account that the FDA assessment times can include a longer period were applicants work on addressing issues brought up in a complete response letter send by the FDA based on a decision that the original application could not (yet) be approved in its present form. In contrast, at EMA this would result in a refusal after the maximum active assessment time was reached. A new marketing authorisation application would then have a restart of the assessment clock.

Figure ACC-2.1: Total assessment times for centrally authorised medicinal products by EMA in days (yearly, 1995-2020)



Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

Figure ACC-2.2: Total assessment times of new active substances/new molecular entities authorised by EMA and FDA in days (yearly, 1995-2020)



Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

Figure ACC-2.1 shows that the total assessment time of EMA centrally authorised products is relatively stable in the period 1995-2020, with no clearly discernible trend in mean and median total assessment times

When comparing EMA assessment times of new active substances with assessment times of new molecular entities authorised by FDA in Figure ACC-2.2 the following trends can be noticed:

- Mean and median assessment times at FDA are longer in the period up to 2010, and the variation in assessment times is larger by FDA compared to EMA, particularly up to 2012. These differences are influenced by the different ways in which the datasets account for refusals. At FDA

assessment times are calculated based on the data from first application to authorisation. At EMA assessment times are calculated as the date of the application that resulted in the authorisation up to the moment of authorisation. Thus, in case an application is refused one or multiple times these assessment times are not included.

- Mean and median assessment times at FDA gradually decrease over time.
- Median review times at FDA are shorter in the period 2016-2020 compared to EMA (median of 244 days at FDA and 343.5 days at EMA)

ACC-6: Number of lead and co-lead assessments by national regulatory authorities (rapporteurs and co-rapporteurs)

Table ACC-6.1 indicates the total number of Rapporteur and Co-Rapporteur roles for initial market authorisations through the centralised procedure per country in the period 1995-2020.

Table ACC-6.1: Number of EMA Rapporteur and Co-Rapporteur roles per country (yearly 1995-2020)

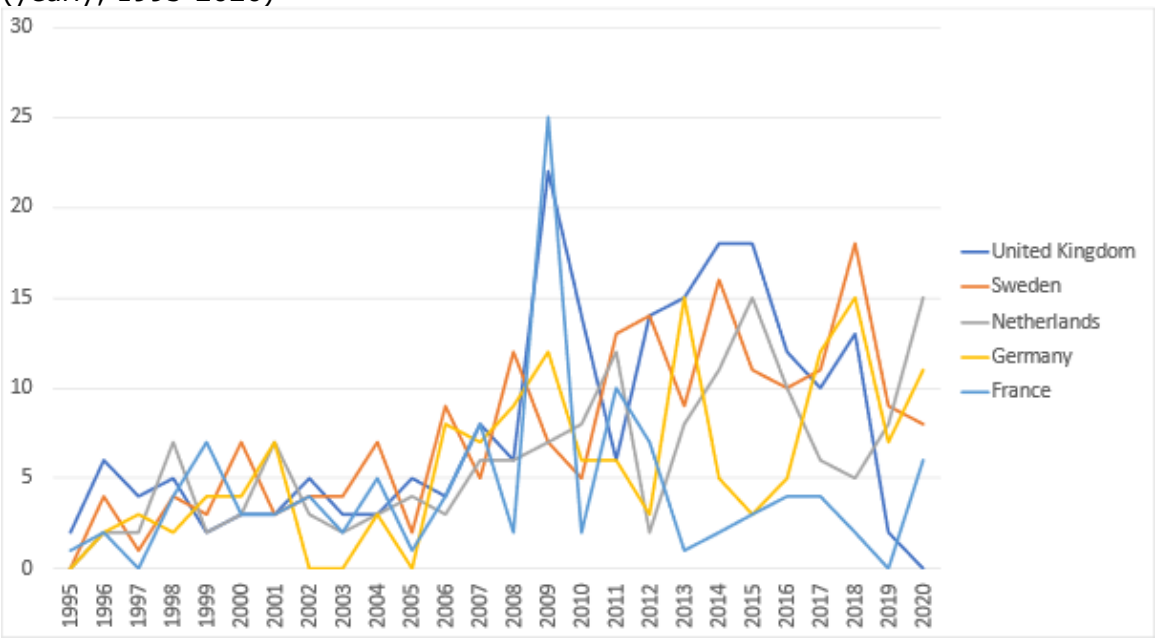
Rapporteur	N	Co-Rapporteur	N
United Kingdom	203	No Co-rap	256
Sweden	196	Germany	117
Netherlands	157	Sweden	100
Germany	149	United Kingdom	97
France	112	France	96
Spain	105	Netherlands	86
Denmark	91	Ireland	79
Ireland	69	Italy	75
Belgium	60	Spain	69
Austria	55	Belgium	68
Portugal	36	Norway	52
Finland	33	Denmark	50
Italy	30	Portugal	46
Malta	26	Austria	46
Czech Republic	23	Finland	44
Estonia	21	Hungary	40
Norway	17	Poland	29
Iceland	14	Estonia	27
Hungary	10	unknown	17
Poland	9	Czech Republic	14
Latvia	7	Greece	12
unknown	7	Luxembourg	10
Slovenia	7	Lithuania	9
Lithuania	6	Latvia	7
Greece	6	Iceland	4
Croatia	4	Romania	3
Slovakia	2	Malta	2
Romania	1	Croatia	1

Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

In addition, for the top 5 (Co-)Rapporteurs overall, a yearly number of (Co-Rapporteur roles is shown in Figures ACC-6.2 and ACC-6.3. The category "No Co-rap" comprises procedures for which no Co-Rapporteur was required (e.g., authorisation of generics) and the category "unknown" comprises procedures for which no Rapporteur has been reported.

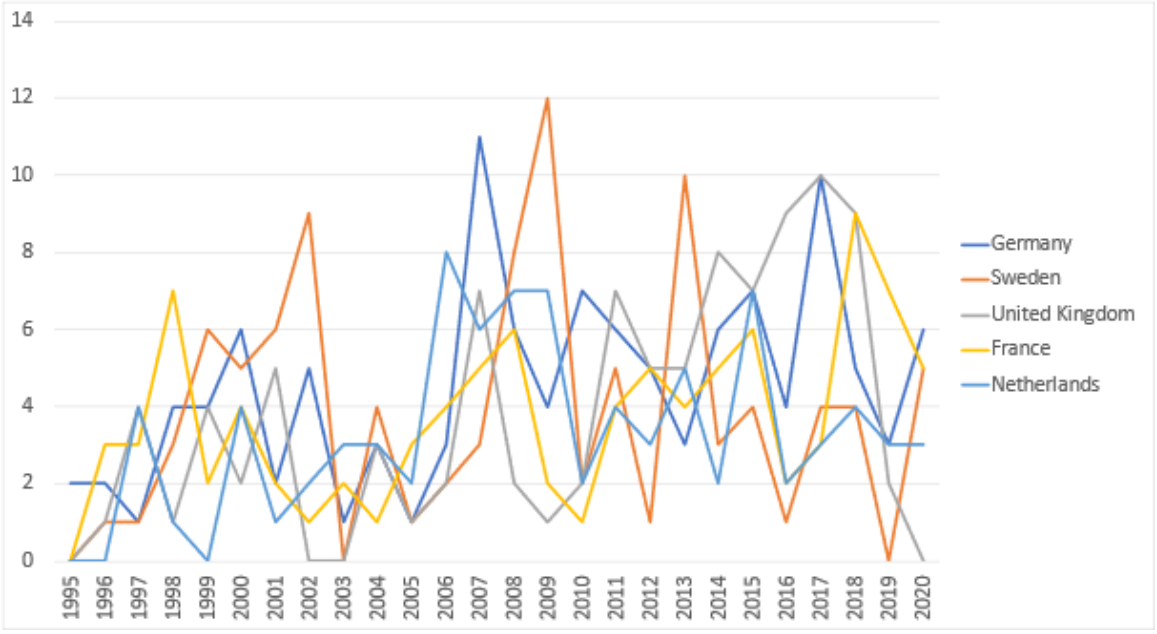
The five countries with the highest number of (co)-rapporteurs for initial marketing authorisations are the United Kingdom, Sweden, the Netherlands, Germany and France.

Figure ACC-6.2: Number of EMA Rapporteur roles for the top 5 Rapporteur countries (yearly, 1995-2020)



Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

Figure ACC-6.3: Number of EMA Co-Rapporteur roles for the top 5 Co-Rapporteur countries over time (1995-2020)



Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

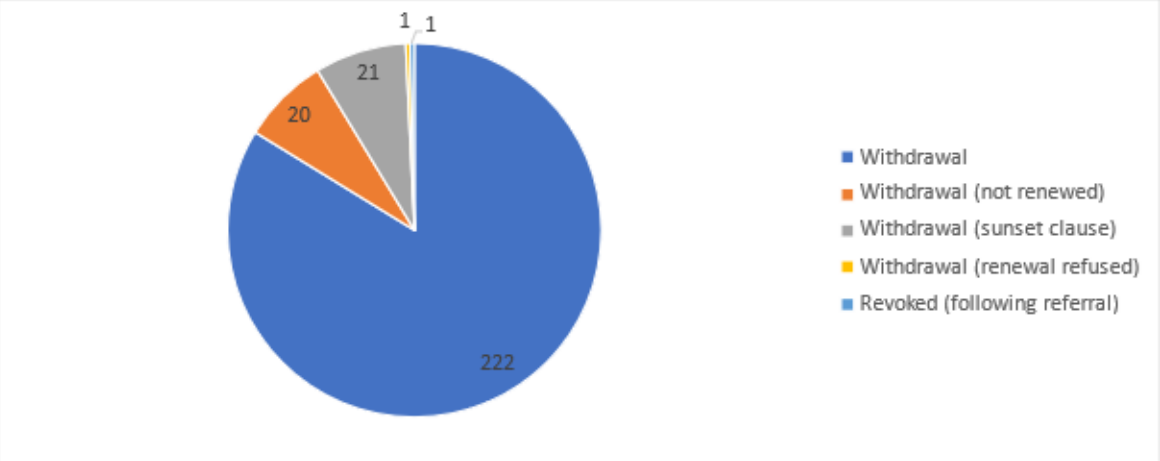
ACC-8: Number of market withdrawals

Figure ACC-8.1 indicates the total number of withdrawn medicinal products initially authorised through the centralised procedure in the period 1995-2020. Withdrawals are recorded in the Union Register of Medicinal Products under 5 different withdrawal types that are mentioned in Figure ACC-8.1. Withdrawals due to non-renewals or the sunset clause are 'passive' withdrawals for which no formal decision-making procedure was initiated.[1]

Figures ACC-8.2 indicates the yearly number of withdrawals by withdrawal type, while Figure ACC 8.3. indicates the number and legal basis of withdrawals. The latter provides insight into withdrawals of products that were approved based on a full application (i.e. article 8(3) of Directive No 2001/83/ec). Figure ACC-8.4 provides an overview of the proportion of medicinal products that were withdrawn as of December 31st 2020 per year of market authorisation.

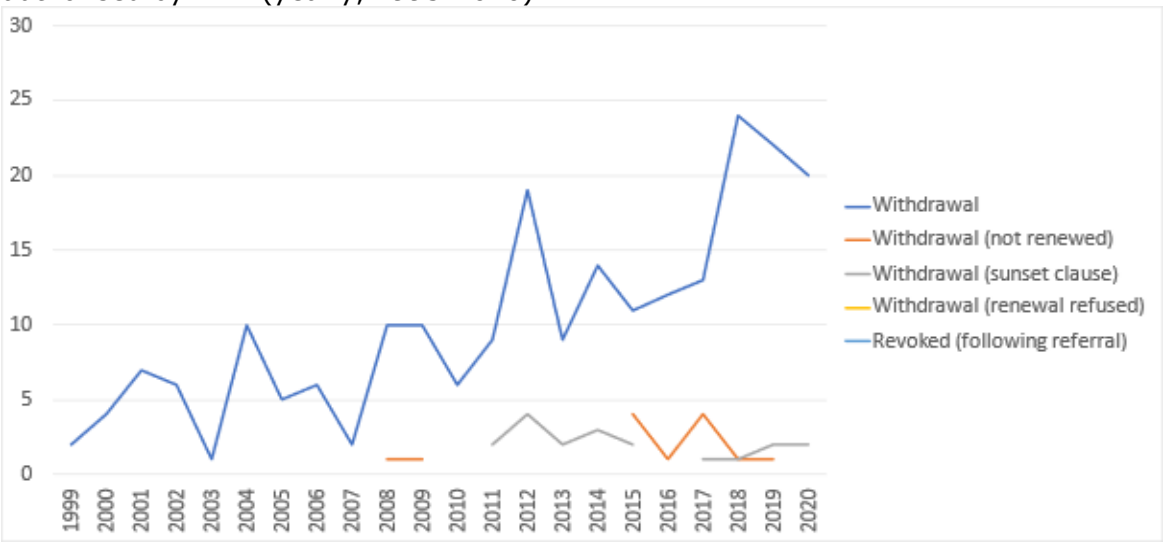
For the matched new active substances that are authorised by both EMA and FDA it was determined whether they were withdrawn in any or both jurisdictions. An overview is provided in Figure ACC-8.5. For FDA withdrawals we rely on the marketing status of new molecular entities in Drugs@FDA[2] and consider a product withdrawn in case the status of a product is discontinued. Publicly available data does not allow us to provide more insight in the reasons for these withdrawals.

Figure ACC-8.1: Total number and type of market withdrawals of medicinal products authorised by EMA (1995-2020)



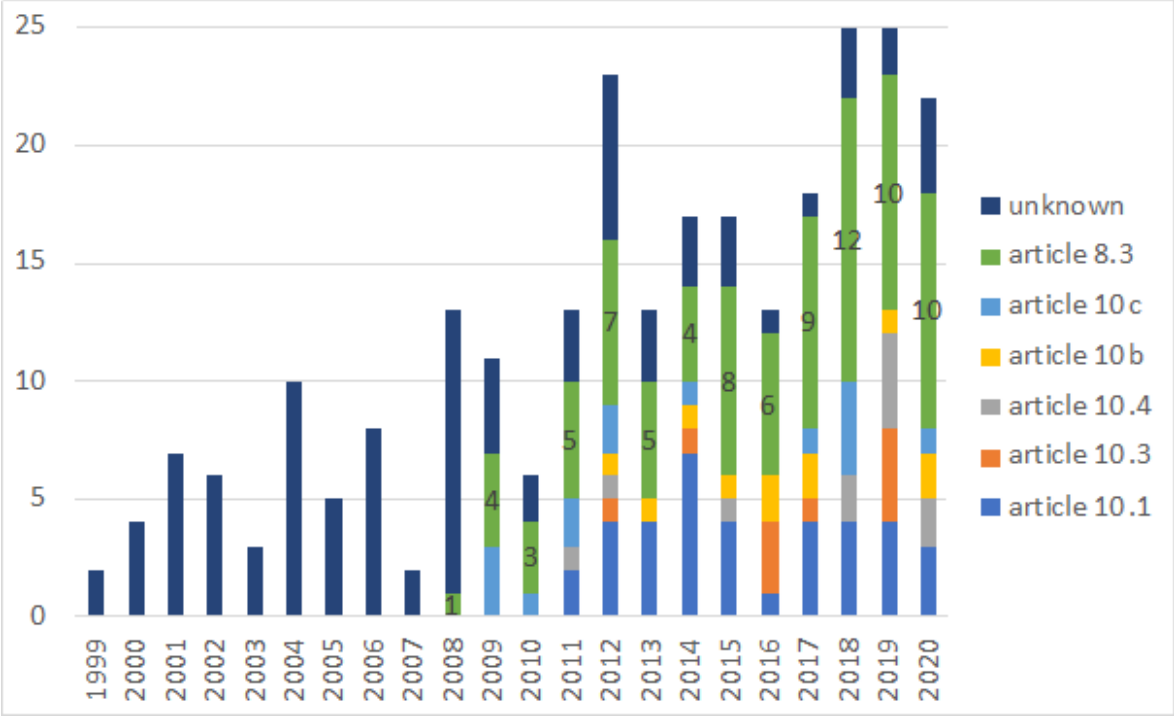
Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

Figure ACC-8.2: Number and type of market withdrawals of medicinal products authorised by EMA (yearly, 1995-2020)



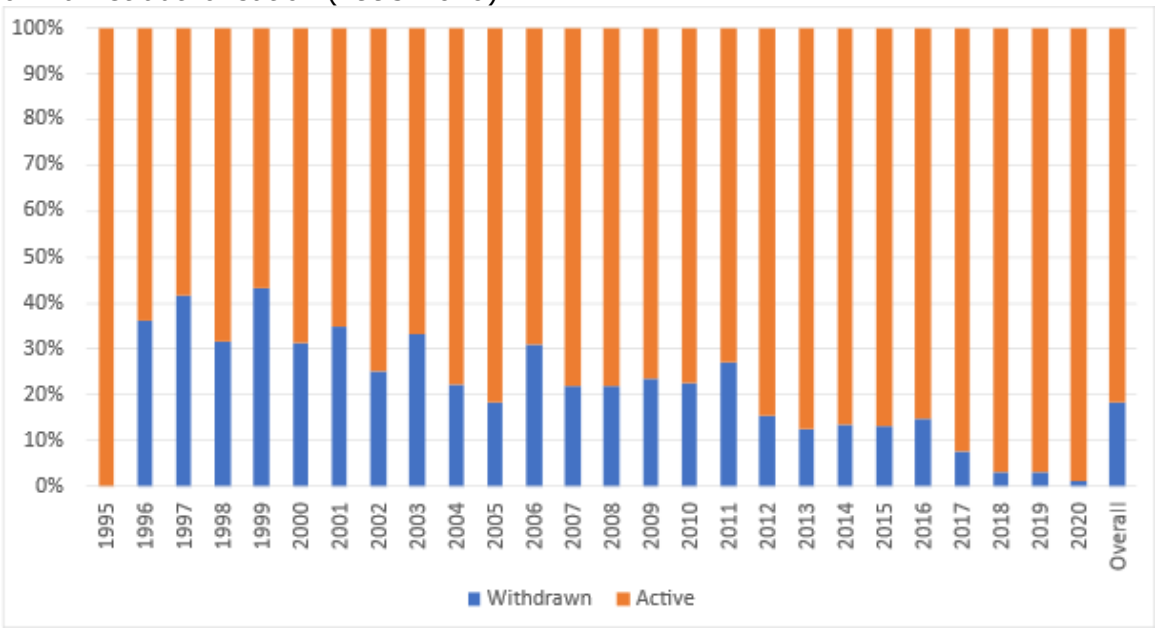
Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

Figure ACC-8.3: Number and legal basis of market withdrawals of medicinal products authorised by EMA (yearly, 1995-2020)



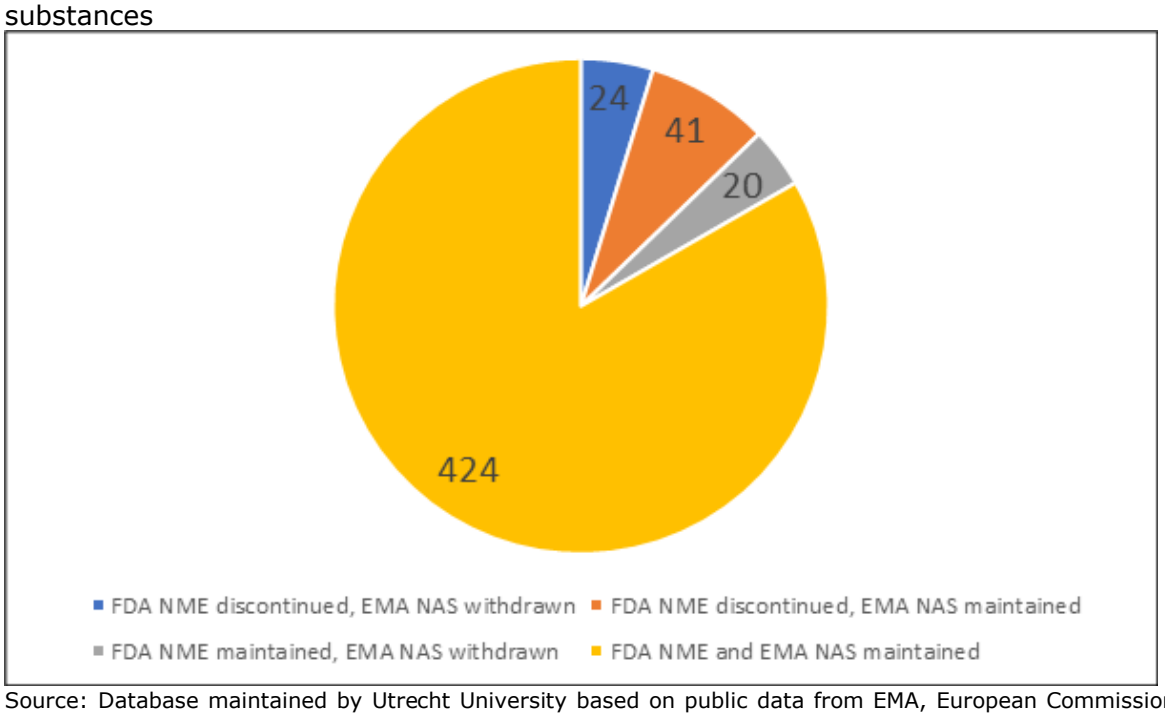
Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

Figure ACC-8.4: Proportion of withdrawn medicinal products authorised by EMA per year of market authorisation (1995-2020)



Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

Figure ACC-8.5: Number of withdrawals by EMA and FDA for matched new active substances



Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

Of all 1,456 EMA centrally authorised products, 265 have been subsequently withdrawn (18.2%). While the number of withdrawals increases over time, the proportion of withdrawals per year of authorisation decreases over time, probably due to an increase in the number of authorised products, yet with shorter follow-up (see below).

Of all 509 centrally authorised new active substances matched with FDA new molecular entities[2], 24 have been withdrawn in both EU and the US. In addition, 20 NASs have only been withdrawn in the EU and 41 NMEs only in the US.

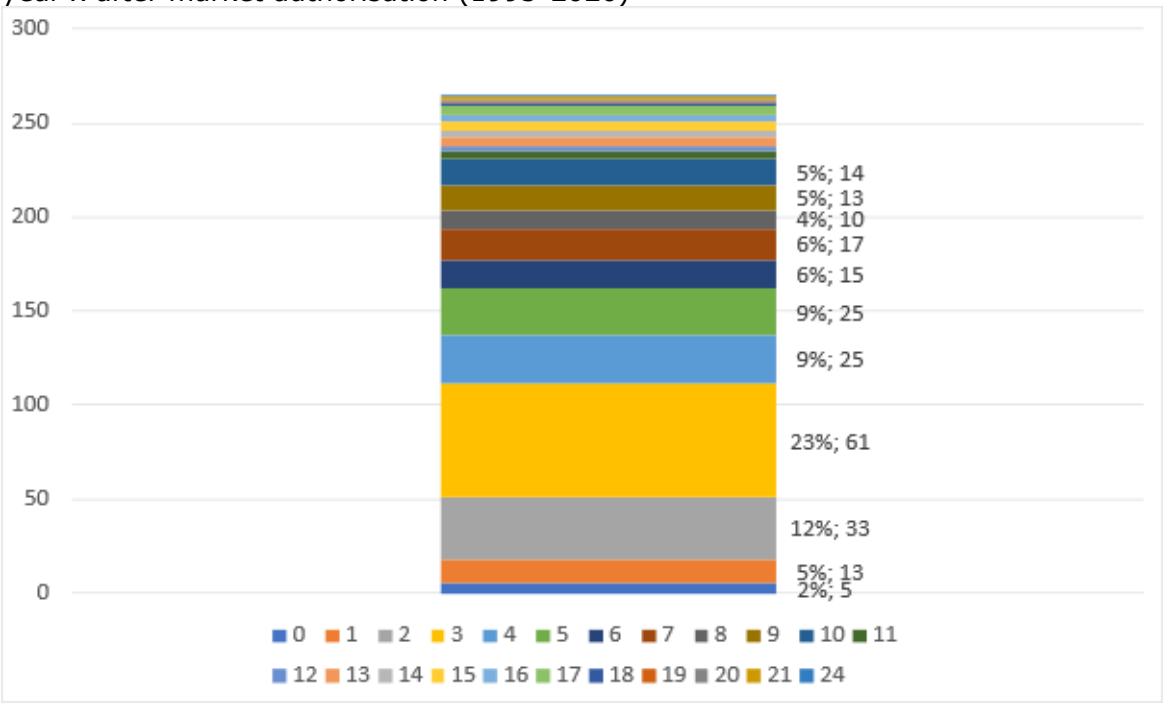
Note that two withdrawal procedures of products are excluded from these figures: one that was renewed anyway one month after withdrawal (NovoNorm) and one that only concerned certain presentations of a product but not the whole authorisation (Daquiran). Two other authorisations that are no longer active concern products that are now integrated as separate presentations of a third authorisation (Humalog-Humaject and Humalog-Pen, integrated in the Humalog authorisation). Since these are not formal withdrawals, these have also not been included in the figures.

ACC-9: Time from marketing authorisation to withdrawal from the market

Figure ACC-9.1 indicates the year after market authorisation in which market withdrawals of medicinal products authorised through the centralised procedure took place. Absolute numbers and percentages are shown for year 0-10 after market authorisation.

Figure ACC-9.2 shows the same data stratified by groups of medicinal products that were authorised in the same year. The absolute number and percentage of withdrawals that took place in the 3rd year after market authorisation are presented as this is the largest category of withdrawals.

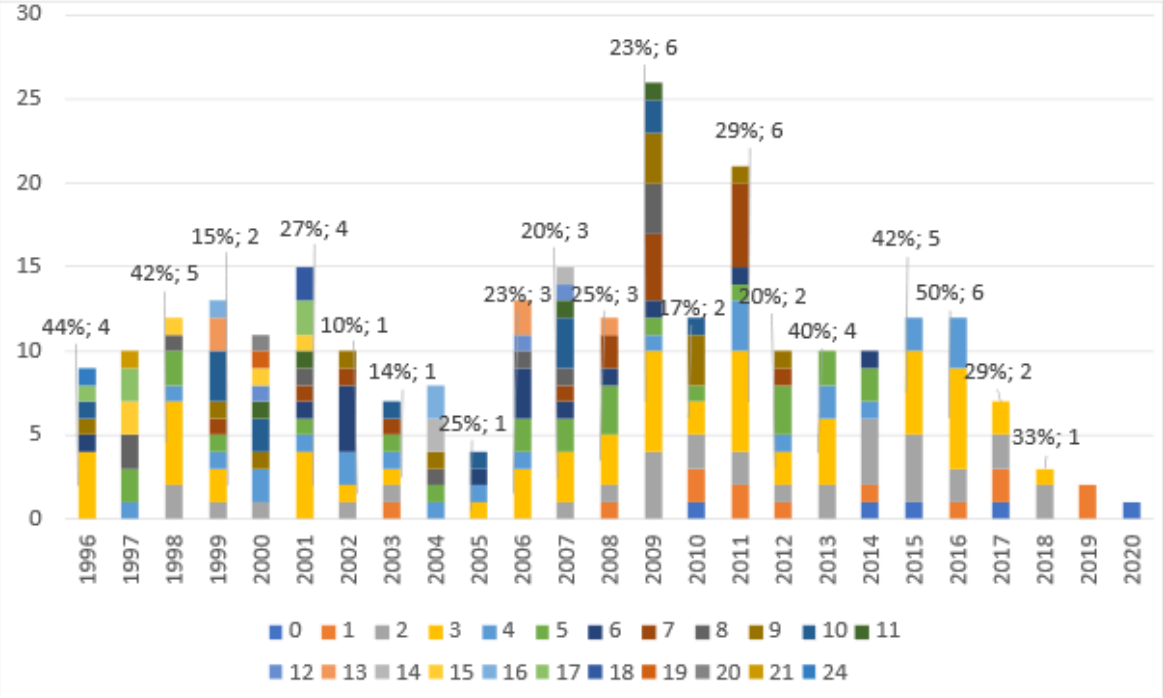
Figure ACC-9.1: Number of medicinal products authorised by EMA and withdrawn in year x after market authorisation (1995-2020)



Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

[2] https://www.accessdata.fda.gov/scripts/cder/daf/

Figure ACC-9.2: Number of medicinal products authorised by EMA and withdrawn in year x after market authorisation (yearly, 1995-2020)



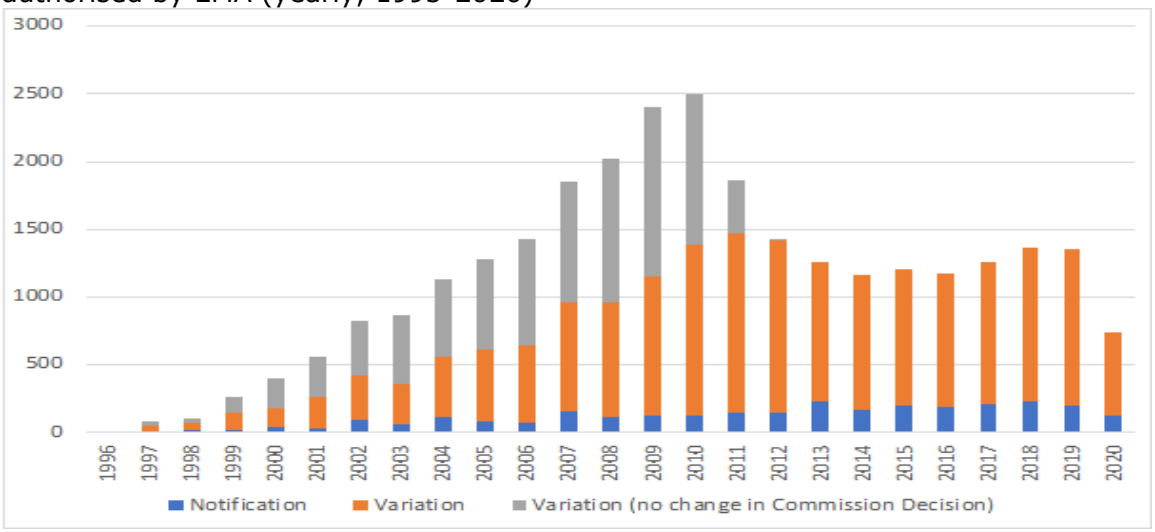
Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

Of 265 market withdrawals, 137 (52%) took place in the first four years after market authorisation – mostly in year 3 (61, 23%). There is no discernible trend over time with respect to early withdrawals in the first four years after marketing authorisation.

ACC-10: Number of Type I and Type II variations

Figure ACC-10.1 indicates the number of notifications and variations in the period 1995-2020. Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Variations without change in Commission Decisions are those that did not affect the terms of the marketing authorisation (e.g., summary of product characteristics, annex II, labelling, package leaflet). Both groups of variations comprise Type IA, Type IB and Type II variations.

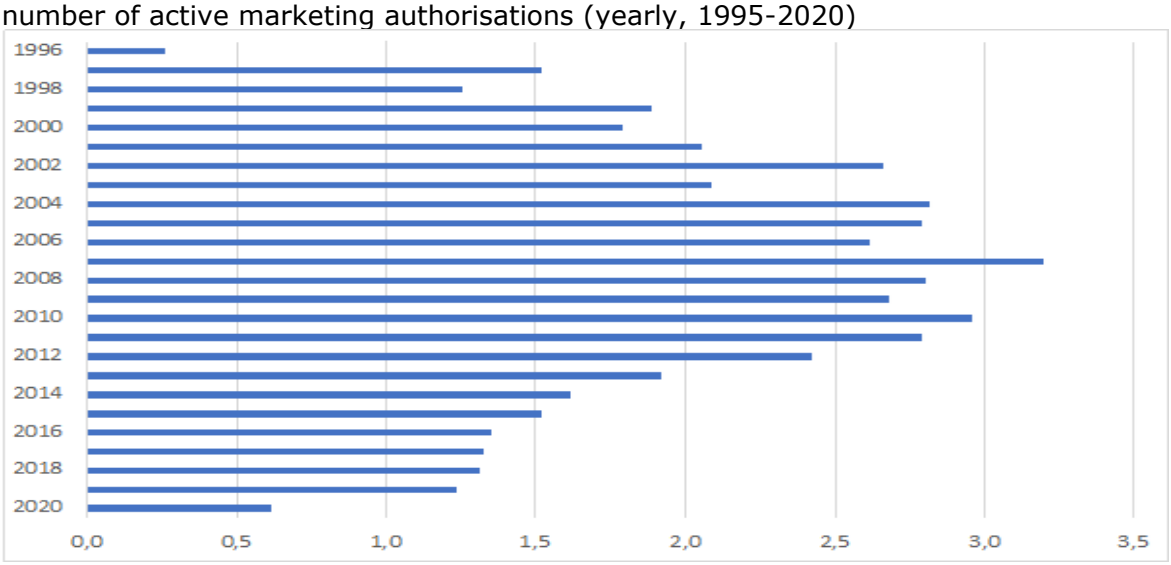
Figure ACC-10.1: Number of Notifications and Variations for medicinal products authorised by EMA (yearly, 1995-2020)



Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

Figure ACC-10.2 indicates the yearly ratio of the number of Notifications and Variations relative to the number of active marketing authorisations. Variations without change in Commission Decision are excluded from this figure and the yearly number of active marketing authorisations is calculated based on the total number of medicines authorised up to and including each year, minus the number of withdrawn medicines up to and including that year.

Figure ACC-10.2: Ratio of the number of Notifications and Variations relative to the number of active marketing authorisations (yearly, 1995-2020)



Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

It is found that in total, 2,939 Notifications, 17,223 Variations and 8,327 Variations without change in Commission Decision occurred between 1995 and 2020.

The yearly ratio of the number of Notifications and Variations and the number of active marketing authorisations increased to 3.2 in 2007 and then steadily decreased to a ratio around 1.2-1.4 in 2016-2019.

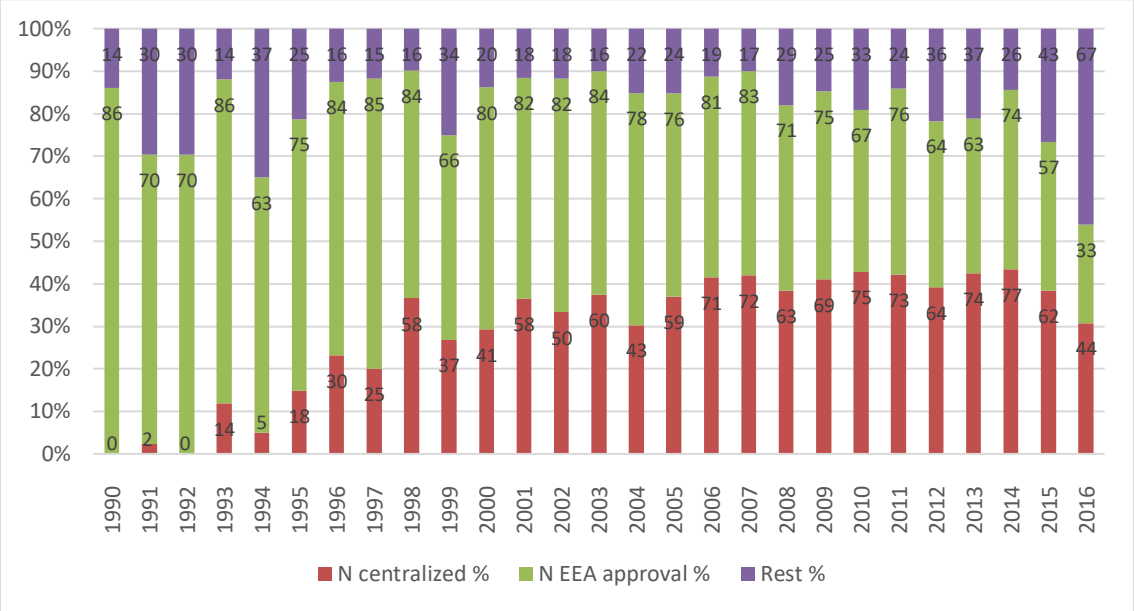
In 2020, a notable drop in both the absolute number of Notifications and Variations and the ratio relative to the number of active marketing authorisations can be observed. This might be a consequence of the COVID pandemic.

Other access indicators from the literature:

Kyle (2019) reports the approval outcomes for new chemical entities (NCEs) that were introduced somewhere in the world from 1990 through mid-2016.[3] The next two figures show the outcomes for new chemical entities (NCEs) that were introduced somewhere in the world from 1990 through mid-2016.

Figure ACC-1.1 shows the share of NCEs that used the EMA's centralized procedure and the share that were launched somewhere in the EEA (N EEA approval), both relative to the number of NCEs first launched in each year. It is worth noting that since 2005 consistently a higher share of NCEs that were launched in the EEA used the centralized procedure relative to the previous years.

Figure ACC-1.1: New chemical entities (NCEs) that were introduced somewhere in the world from 1990 through mid-2016



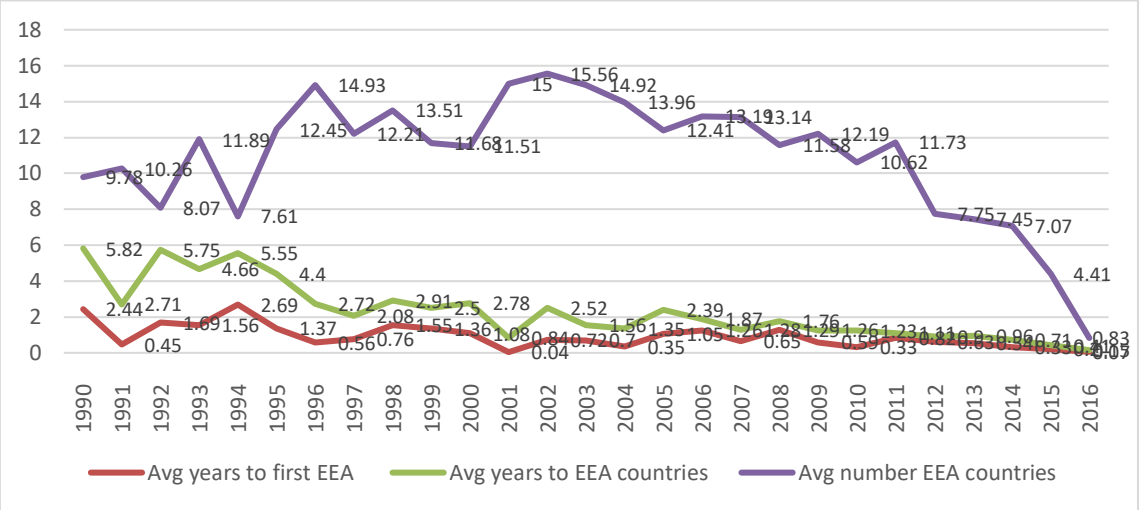
Source: Kyle (2019), using data from IQVIA-MIDAS and EMA.

Figure ACC-1.2 shows the average lag between the first global launch and the first EEA launch (Average years to first EEA), the average lag between the first global launch and all EEA countries in which the drug was eventually introduced (Avg years to EEA countries), and the number of countries where these drugs are launched (Avg number EEA countries).

Figure ACC-1.2 shows that over the years, the average time to approval across the EEA (conditional on launch) has fallen, and the average number of EEA countries in which a product is launched has decreased in the last years. However, there is no clear 'jump' in 2005 (apart from a slightly lower number of NCEs launched using the centralized procedure in 2004, relative to 8 years before and after) that could indicate an impact of the 2004 revision of the general pharmaceutical legislation in any of the outcomes.

[3] Kyle, M. The Single Market in Pharmaceuticals. Review of Industrial Organization. 2019. Vol. 55, no. 1, p. 111–135.

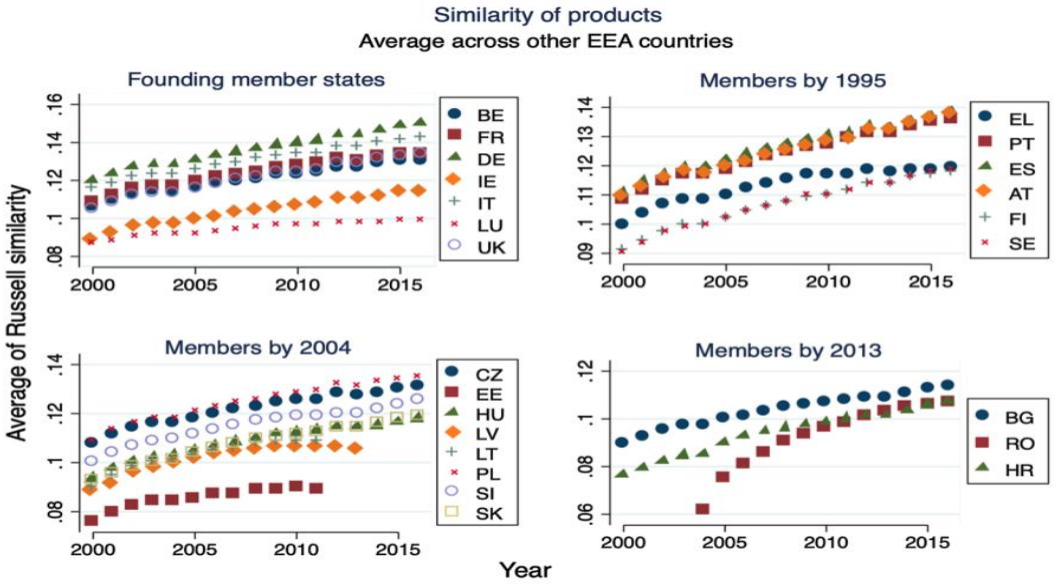
Figure ACC-1.2: Outcomes for new chemical entities (NCEs) that were introduced somewhere in the world from 1990 through mid-2016



Source: Kyle (2019), using data from IQVIA-MIDAS and EMA.

Kyle (2019) also investigates whether pharmaceutical product markets in the EU had increased in similarity over time (Figure ACC-1.3). To assess this, she calculates the Russell–Rao binary similarity coefficient for all possible country pairs[4]. As shown in the next figure, from 2000 to 2016, the average similarity between a country and other member states has grown over time, yet there is no change in the trends that can be attributed to the 2004 revision of the general pharmaceutical legislation.

Figure ACC-1.3: Average product similarity between a country and other MS



Source: Kyle (2019), using data from IQVIA-MIDAS and EMA.

[4] This coefficient measures the proportion of pharmaceutical products that are available in both countries out of all products available somewhere in the sample of countries.

1.4 AFFORDABILITY AND SINGLE MARKET INDICATORS

Indicator name	Indicator description
AFF-1	Net price of selected group of medicines (e.g., representative sample or essential medicines list) in individual countries
AFF-2	Ratio of net price of medicines to GDP per capita in individual countries
AFF-3	Expenditure on medicines in total healthcare spending in individual countries
AFF-4	Rate of generics/biosimilars entry and uptake
AFF-5	Time to entry after IP protection expires*
AFF-6	Average price discount (%) of generics/biosimilars over originator*

* Note that these indicators were not calculated

For the analysis of indicators AFF-1, AFF-2 and AFF-4 we employed the IQVIA MIDAS dataset containing information on disaggregated drug sales in different countries. The data were provided in two distinct datasets: while the 'historical' dataset covers the 2002 – 2009 period, the 'current' dataset contains data from the last quarter of 2009 until the end of 2020. Thus, the joint dataset covers the 19 years period from 2002 to 2020 at a quarterly time resolution.

We observe a total of 221,877 individual drugs being sold in up to 38 different countries (data are available for the following countries: Australia, Austria, Belarus, Belgium, Bosnia, Bulgaria, Canada, Croatia, Czech Republic, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Japan, Kazakhstan, Korea, Latvia, Lithuania, Luxembourg, Netherlands, Norway, Poland, Portugal, Romania, Russia, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, UK and USA), resulting in a total of 384,078 time-series' of drug sales at the country level. The final dataset contains around 19.5m observations.

For these drugs, we observe the quantity and revenue sold in a country and quarter, allowing us to calculate approximate (see caveats below) prices. Further, we can distinguish biological and non-biological drugs, generics and branded products, as well as observe a drugs' active molecule. This allows us to link branded products to their subsequent generic versions to investigate price discounts and time to entry.

In most analyses EU countries (Austria, Belgium, Bulgaria, Croatia, Czech Republic, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, UK) are compared to either i) all other available countries (see list above) or ii) to a selection of relevant comparators, specifically Australia, Canada, Japan, Korea, Switzerland and the US.

Caveats

Price data without discounts: The revenues and prices reported in the IQVIA MIDAS data do not account for any price discounts from vendors or manufacturers. They also do not account for the fact that a large share of drug expenses is borne by social security systems in most of the countries surveyed.

Joining of current and historical datasets: to extend the analysis to the period before 2010, two separate and non-coherent dataset had to be joined. This results in two main issues. First, only around 1/3 of the time series of drug sales could be matched across the two datasets, the remaining drugs exist independently in the 'historical' and 'current' datasets. This can result in a 'jump' at the point where the two datasets are joined. Secondly, the recording of sales and quantities are not coherent in the historical data and the first period of the current dataset. This results in a 'kink' in the third quarter of 2009, which has been largely eliminated through interpolation from the previous and subsequent period, but is still visible in some of the graphs.

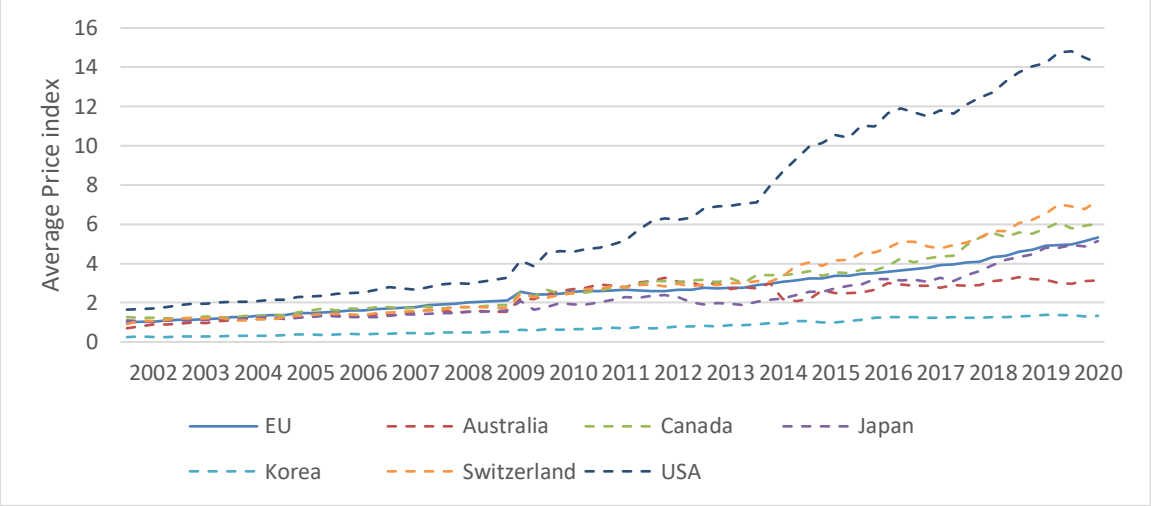
Data aggregation: For the purposes of the analysis, data were aggregated to the drug/country level. Particularly, sales of the same drug across different ATC classes were added up.

Backward interpolation of drug attributes: Some drug attributes (e.g. whether a compound is generic or branded) are not available in the historical data. For the subset of drugs where current and historical data could be linked, these attributes were 'backwards interpolated' from the current to the historical data.

AFF-1: Net price of selected group of medicines (e.g., representative sample or essential medicines list) in individual countries

The goal of this indicator is to track the evolution of drug prices over time and compare the situation in the EU with that of comparator regions. Specifically, the average price of drugs over time in the EU will be compared to prices in Australia, Canada, Japan, Korea, Switzerland and the US. Figure AFF-1.1 calculates average prices for all EU countries and compares them to the other regions. For the average prices, all available drugs (i.e., more than 200,000 different products) are employed and the price per standardized unit is normalized to "1" in the EU in the first quarter of 2002.

Figure AFF-1.1: Average price of all drugs



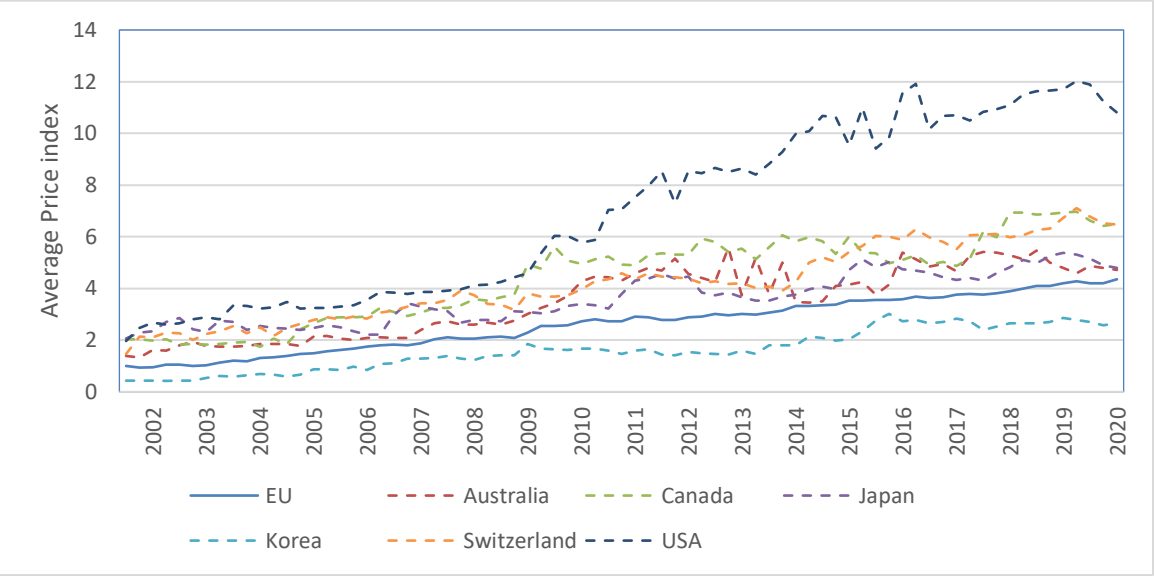
Source: IQVIA-MIDAS

Figure AFF-1.1 shows that the initial level of prices in the EU is intermediate: while lower than in the US and Canada, it is higher compared to Australia and Korea and similar to Japan and Switzerland. The dynamics of the graph show two extreme cases of price evolution. In Korea, prices remain constantly low and increase only moderately over the whole sample period. On the other hand, in the US, price increase rapidly, particularly after 2009, and increase almost tenfold over the sample period. The evolution in Europe is intermediate. Prices increase steadily, reaching about five times their 2002-level in

2020 (the small spike in 2009 is due to the joining of the datasets and should be disregarded, see "Caveats"). The increase in prices seems to slightly increase after 2017 and rather similar developments can be observed for Switzerland, Canada and Japan.

Figure AFF-1.2 follows the same logic, but restricts the price averages to key drugs, the total sales of which exceed a revenue of 10m €. Only 193 drugs fall in this category. Thus, the graph focuses on the commercially top-selling drugs across all countries. While the resulting picture is similar to the one before, the price growth of drugs in the EU is now visibly below that of other comparators, except for Korea. Thus, while the price increases in the EU are similar to most comparator regions (except the US and Korea) when looking at all drugs, price increases in the EU are relatively lower when focussing on the most commercially successful drugs.

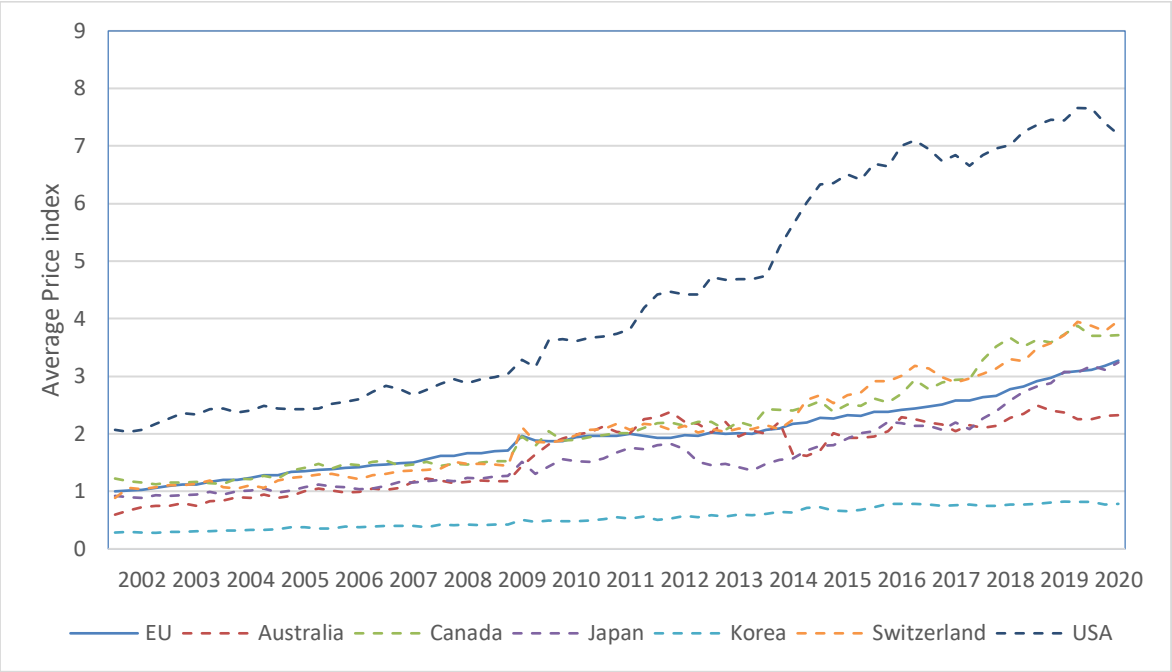
Figure AFF-1.2: Average price of key drugs



Source: IQVIA-MIDAS

Figure AFF-1.3 focuses on the price evolution of relatively expensive drugs. These correspond to the highest price-quartile in each country. Thus, for each country, we calculated the average price of each drug and selected the most expensive quarter of the data. The resulting graph is very similar to the first graph, containing the average prices of all drugs. This suggests that the overall price evolution is driven by the relatively expensive drugs.

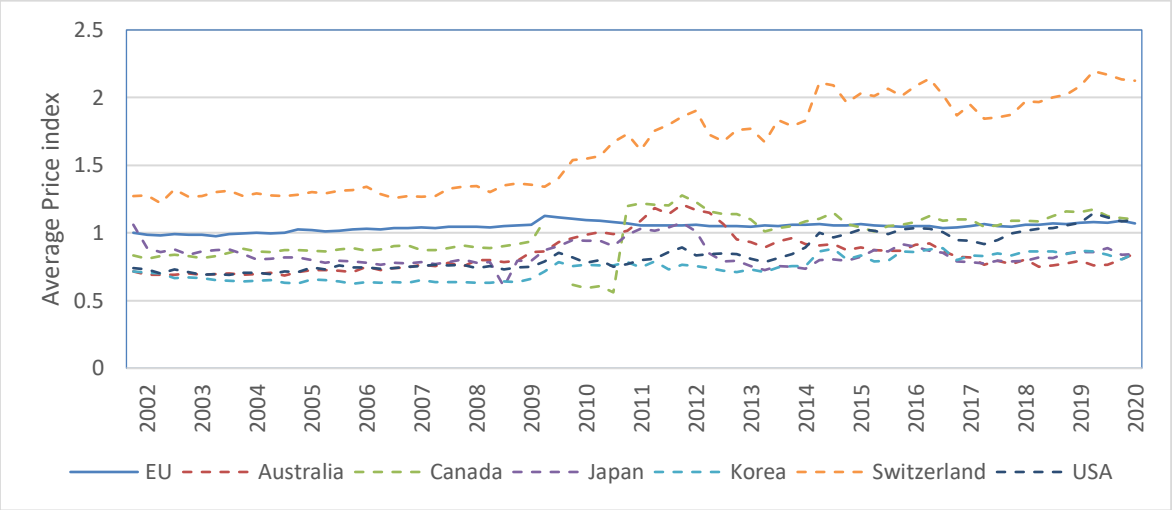
Figure AFF-1.3: Average price of high-price drugs



Source: IQVIA-MIDAS

This intuition is corroborated by Figure AFF-1.4, which illustrates the price evolution of relatively cheap drugs, corresponding to the first quartile of the distribution of average drug prices. While the resulting time series is somewhat noisy for some comparators, it is almost completely flat for the EU, suggesting that the prices of these drugs have risen by only about 10% on average over the sample period.

Figure AFF-1.4: Average price of low-price drugs



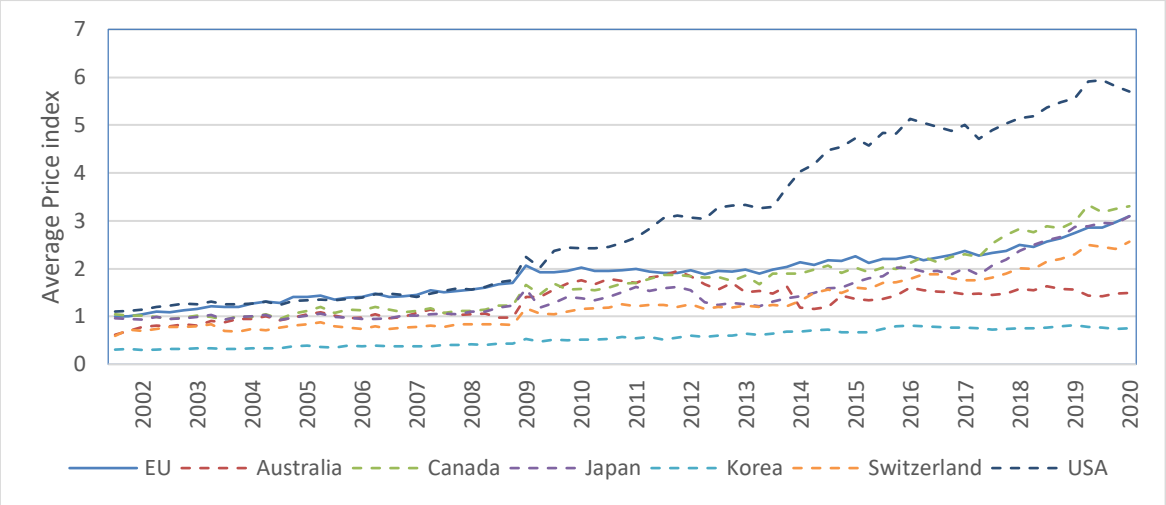
Source: IQVIA-MIDAS

AFF-2: Ratio of net price of medicines to GDP per capita in individual countries

AFF-2 is similar to AFF-1 in that it plots the average prices in different regions over time. It differs insofar, as price are normalized by the GDP per capita in the respective regions. Thus, instead of calculating changes in nominal prices, the evolution of prices is calculated accounting for differences in wealth across the regions compared. Data on GDP per capita is obtained from the World Bank.

As before, we compare four different baskets of drugs: all drugs available, the top-grossing (>10m €) drugs, as well as the most expensive and the most affordable quarter of drugs. The evolution of all drug prices relative to GDP per capita is similar to the non-GDP-adjusted graph shown earlier, but also contains some interesting differences. First, the overall increase in drug prices is more moderate in real terms than in nominal terms. While the increase in nominal prices in the EU was about five-fold, real prices have increased by a factor of approximately two and a half. The situation is similar for the comparators. Thus, while the increase is lower in real terms, it is still substantial. Second, while the EU was in the middle field of price increases in nominal terms, it now ranks only behind the US and Canada. Thus, in real terms, price increases were larger in the EU than in Switzerland.

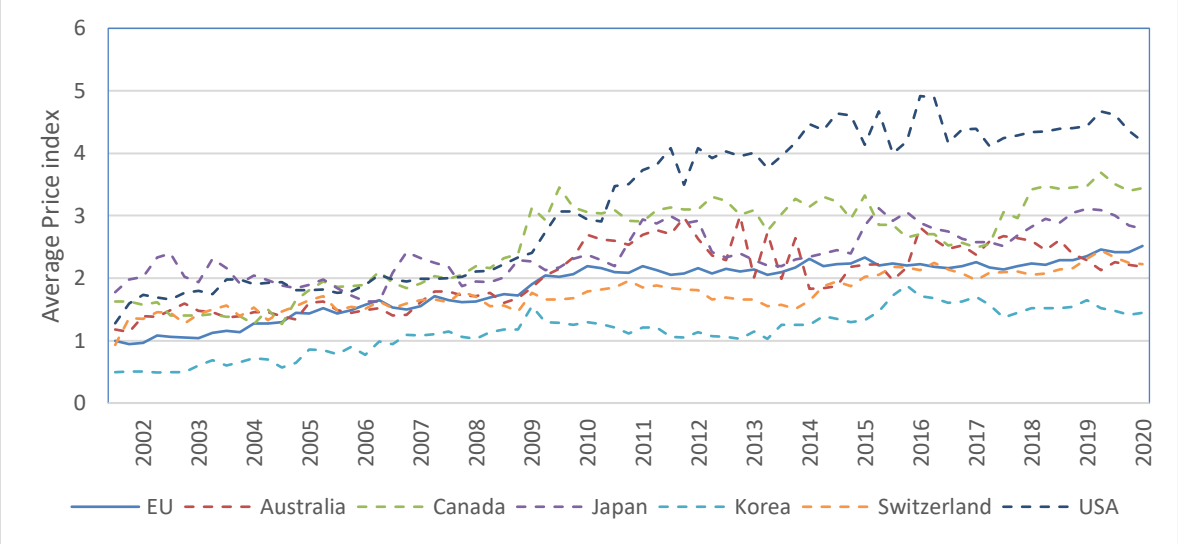
Figure AFF-2.1: Average price of all drugs relative to DGP per capita



Source: IQVIA-MIDAS

When looking at the most commercially successful drugs in the next graph, the situation is quite similar to before. Again, the EU's price growth is relatively higher compared to the nominal scenario, but it remains in the middle field of comparator regions.

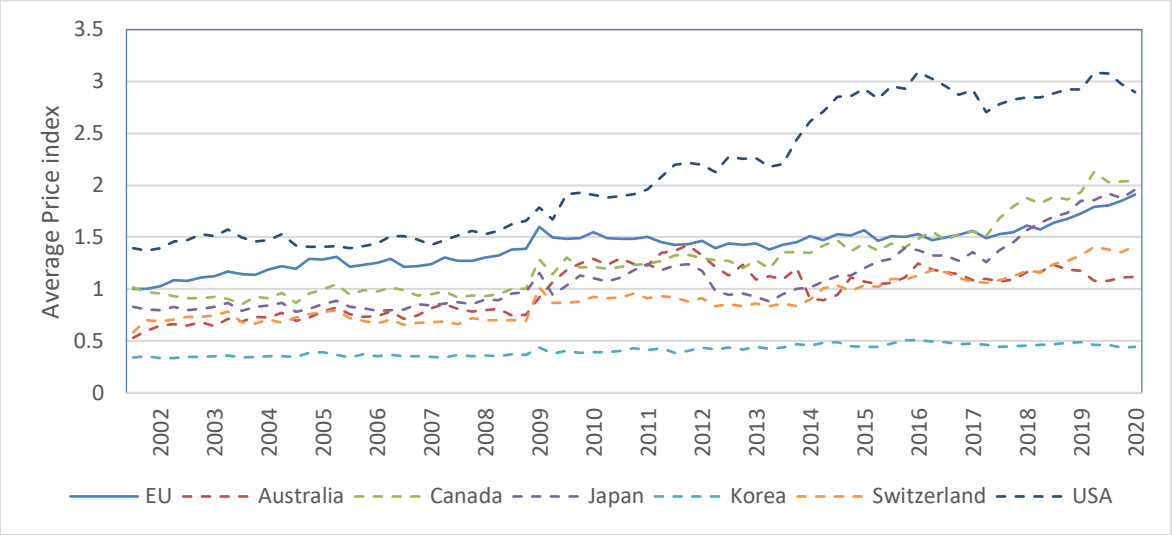
Figure AFF-2.2: Average price of key drugs relative to GDP per capita



Source: IQVIA-MIDAS

Focussing on high-price drugs yields a picture that is comparable to the nominal case, with price increases scaled down. The average, real price of high-price drugs has approximately doubled in the EU over the sample period.

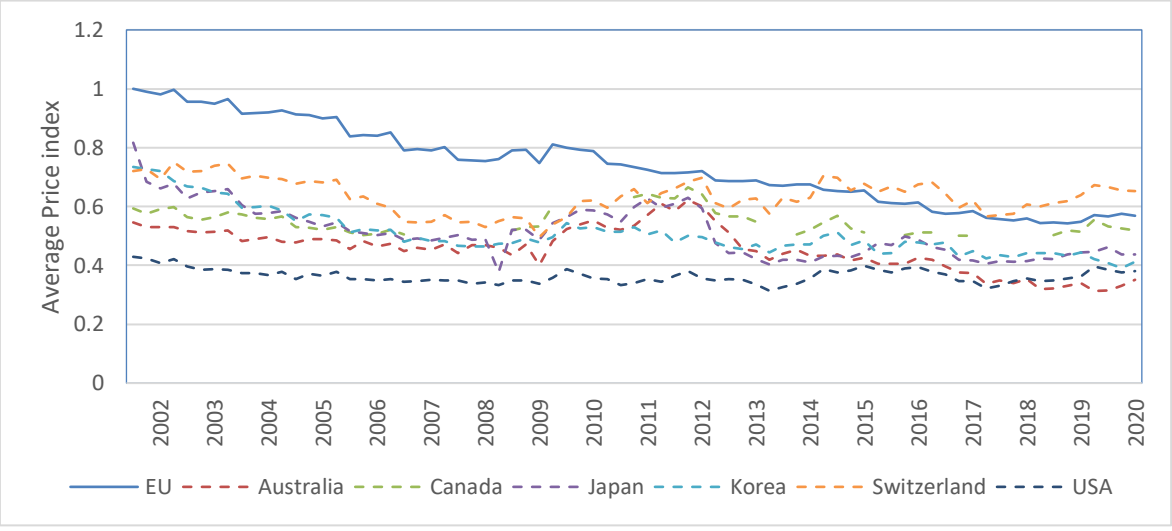
Figure AFF-2.3: Average price of high-price drugs relative to DGP per capita



Source: IQVIA-MIDAS

Interestingly, the price increases of low-price drugs seem to be below GDP growth on average, such that their real prices decline. The average, real prices of these drugs are decreasing over the sample period in the EU and all comparator regions, except for the US. In the US, these drugs start at a price level substantially below that in the EU and other regions and remain mostly constant. In all other regions, price decline, with the decline being most accentuated in the EU. Here, the real prices of these low-cost drugs have declined by more than a third over the sample period.

Figure AFF-2.4: Average price of low-price drugs relative to DGP per capita



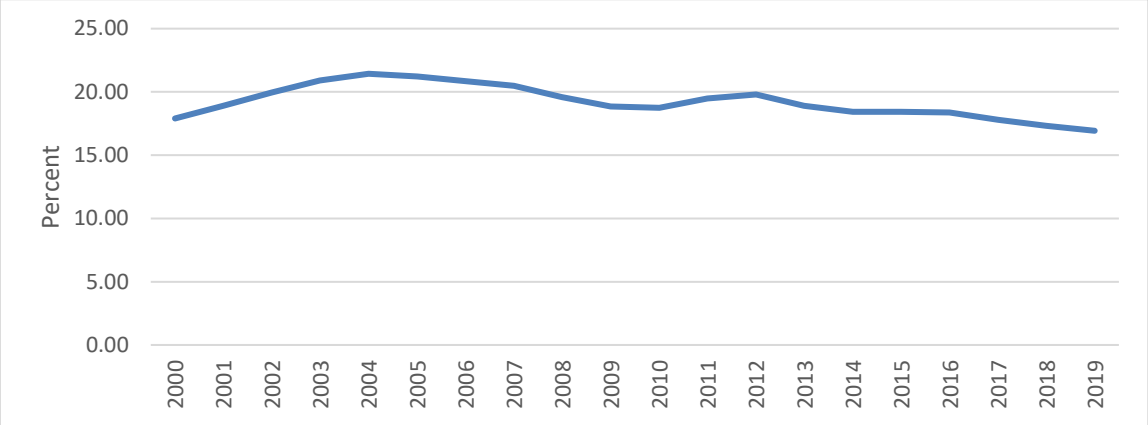
Source: IQVIA-MIDAS

AFF-3: Expenditure on medicines in total healthcare spending

We find that in the EU, average drug spending as a percentage of health spending stood between 17–21% during the last 20 years. While this share was higher in 2003- 2007 it decreased slightly in the last 12 years. The figure is in line with the findings of a recent

report by the IQVIA institute that highlights that drug spending has been growing more slowly than health spending in recent periods in most countries.[5]

Figure AFF-3: Average share of pharmaceutical expenditures in total health spending in EU27 and UK



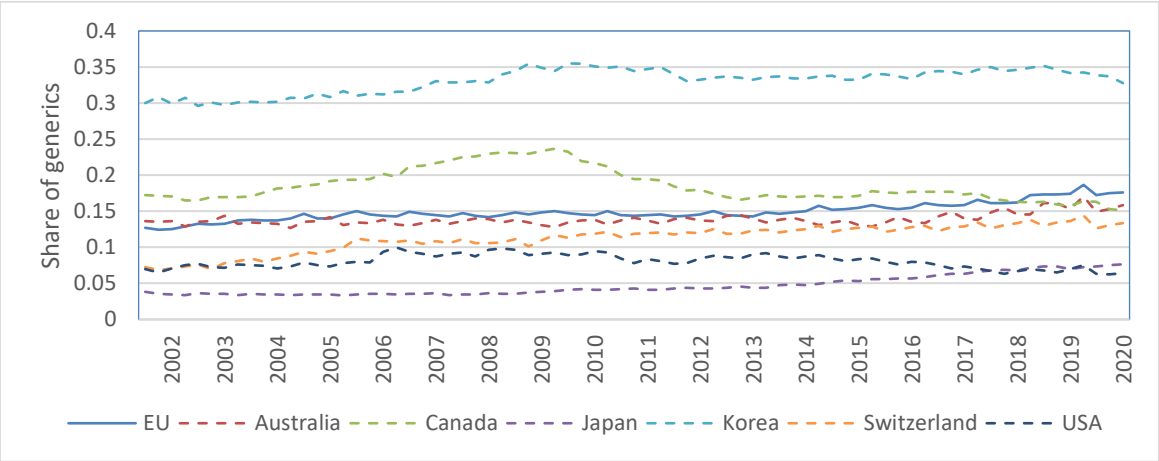
Source: OECD Health Statistics. Average across countries is not a weighted average. Pharmaceutical spending covers expenditure on prescription medicines and self-medication, often referred to as over-the-counter products. In some countries, other medical non-durable goods are also included. Pharmaceuticals consumed in hospitals and other health care settings are excluded. Final expenditure on pharmaceuticals includes wholesale and retail margins and value-added tax. This indicator is measured as a share of total health spending.

AFF-4: Rate of generics/biosimilars entry and uptake

This indicator aims to assess the importance of generics in the EU and comparator regions. Unfortunately, the information of whether a product is branded or generic is only available for the current dataset, but not for the historical one (up to 2009). This has been addressed by matching current and historical drug products via their name and extrapolating their branded/generic status from the current to the historical dataset. This approach successfully links about one third of drugs across datasets.
Figure AFF-4.1 shows that the share of generics in total drugs sales is increasing in the EU and most comparator regions. The share of generics has been rising in the EU over the whole sample period, but with a rather modest rate of growth.

[5] In Aitken., et al. (2021), drug spending as a percentage of health spending is inclusive of all products and locations where they can be delivered (retail, hospitals) and are reported after discounts and rebates received by payers.

Figure AFF-4.1: Share of generics in total drug sales

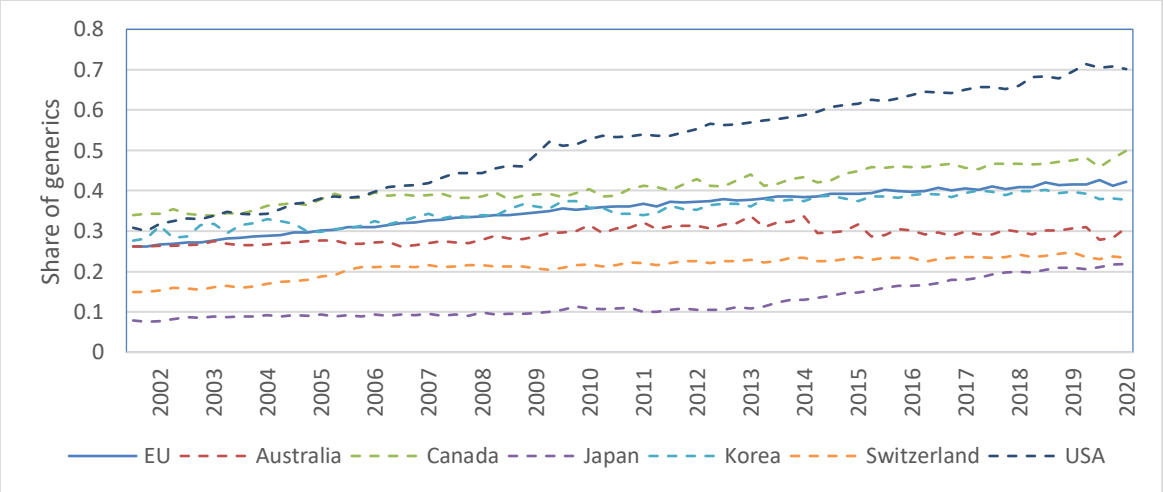


Source: IQVIA-MIDAS

As the prices of generic drugs are usually much lower than those of branded drugs, it might be misleading to only look at sales data when assessing the degree of generics adoption. In the MIDAS dataset, the imputed price of generics per unit is, on average, four times lower than that of branded products. Thus, in order to avoid understating the relevance of generics due to their low price, we repeat the analysis above using the share of generics in total consumption rather than their share in total sales.

Figure AFF-4.2 shows that generics consumption as a share of total consumption is highest in the US, reaching almost 80% of total consumption at the end of the sample period. The rise of generics consumption in the US is almost continuous, rising from around 30% in 2002 to around 70% in 2020. The EU and most other comparators also experience a rise in the share of generics, but at a lower growth rate. The share of generics in total consumption in the EU reaches around 50% at the end of the sample period, up from approximately a quarter at the beginning. The trajectory is quite similar to those of Canada and Korea. Australia, Japan and Switzerland consume generics to a lesser degree.

Figure AFF-4.2: Share of generics in total consumption



Source: IQVIA-MIDAS

1.5 SINGLE MARKET INDICATORS

Indicator name	Indicator description
	Shortage-related indicators:
SM-1:	Trend of shortage duration for medicines in shortage
SM-2:	Trend of volume drop for medicines in shortage (critical, severe, moderate)
SM-3:	Change of root cause reported for medicines
SM-4:	Proportion of generic products in shortage
	Therapeutic area competition:
SM-5:	Number of authorised medicines per class, therapeutic area
SM-6:	Number of pipeline products per class, therapeutic area

SM-1: Trend of shortage duration for medicines in shortage

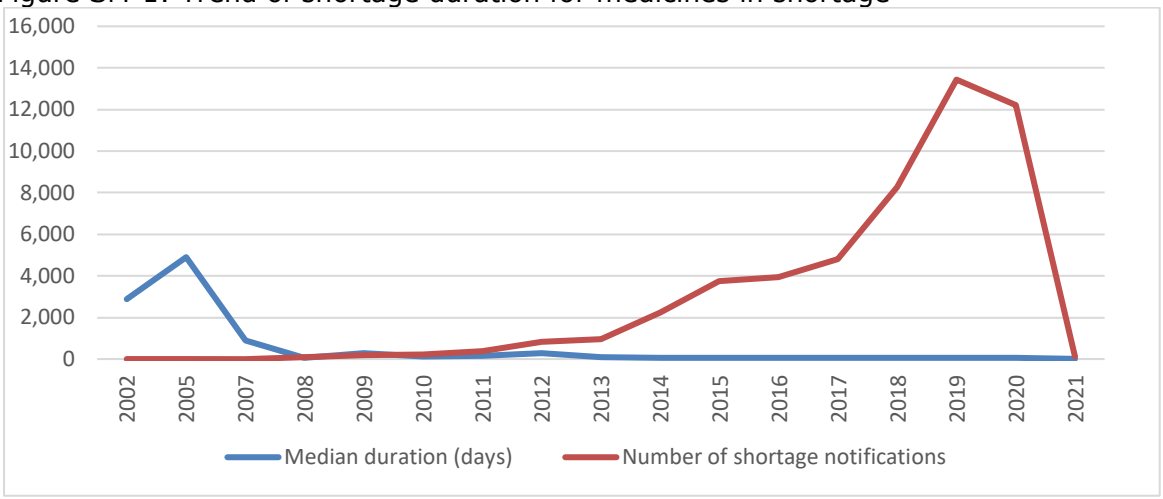
Medicine shortages occur when the quantity demanded is greater than the quantity supplied at the market price. There are two main causes of shortages—increase in demand or decrease in supply. It is useful to distinguish between short and more sustained medicine shortages as they may differ in their root causes. Longer shortages may be more likely to be caused by manufacturing and quality issues, as these sorts of issues can take weeks or even months to be resolved. By contrast, shortages that are caused by, for instance, supply quotas or incorrect forecasting may be resolved more quickly as they reflect problems with local availability rather than with overall supply. To understand the typical duration of drug shortages in the EU, we use data from the study "Future-proofing pharmaceutical legislation: study on medicine shortages".[6]

Figure SM-1 shows that while the number of shortage notifications has increased substantially and persistently since 2013, reaching its peak in 2019 with close to 14,000 notifications, the median duration of shortages remains close to 102 days on average during the period 2008-2021. However, these trends should be interpreted with caution since most countries only reported data on shortages notifications from 2018 onwards. On the other hand, the apparent reduction in the median shortages duration since 2007 is explained by the fact that very few shortages were reported before 2007 and those are unusually long-lasting ones.

Table SM-1 shows the median shortage duration for medicines by ATC1 code during the period 2007-2021 (with the majority being reported during 2017-2020). Medicines for the cardiovascular system as well as dermatologicals report the highest median shortage durations (246 and 238 days, respectively).

[6] https://data.europa.eu/doi/10.2875/211485

Figure SM-1: Trend of shortage duration for medicines in shortage



Source: Technopolis Group, based on sales data from the IQVIA MIDAS database and shortage notifications by NCAs. The average number of countries reporting data on notifications during 2002-2010 is 2; from 2011-2013 is 7; and, from 2014-2021 is 15. The average number of countries reporting data on shortages duration for 2002-2010 is 2; from 2011-2013 is 4; and, from 2014-2021 is 11.

Table SM-1: Median shortage duration for medicines by ATC1 code

ATC1	ATC code description	Median duration (days)	Min. duration (days)	Max duration (days)
A	Alimentary tract and metabolism	183	1	5388
B	Blood and blood forming organs	168	1	5145
C	Cardiovascular system	246	1	5793
D	Dermatologicals	238	1	3723
G	Genito-urinary system and sex hormones	213	1	5969
H	Systemic hormonal preparations (excluding sex hormones)	114	3	5586
J	General anti-infectives systemic	184	1	5983
K	Hospital solutions	129	7	4998
L	Antineoplastic and immunomodulating agents	151	1	5587
M	Musculo-skeletal system	184	1	4828
N	Nervous system	198	1	5930
P	Parasitology	92	2	2045
R	Respiratory system	119.5	1	4974
S	Sensory organs	148	2	5353
T	Diagnostic agents	226	7	5083
V	Various	138	7	3982
Total		**187**	**1**	**5983**

Source: Technopolis Group, based on sales data from the IQVIA MIDAS database and shortage notifications by NCAs.

SM-2: Trend of volume drop for medicines in shortage (critical, severe, moderate)

Most countries define a shortage simply as any situation whereby supply does not meet demand, but do not define how wide the gap between the two must be before a notification must be made. To better understand the extent of product shortages and their impact on overall product availability we use the analysis presented in the study

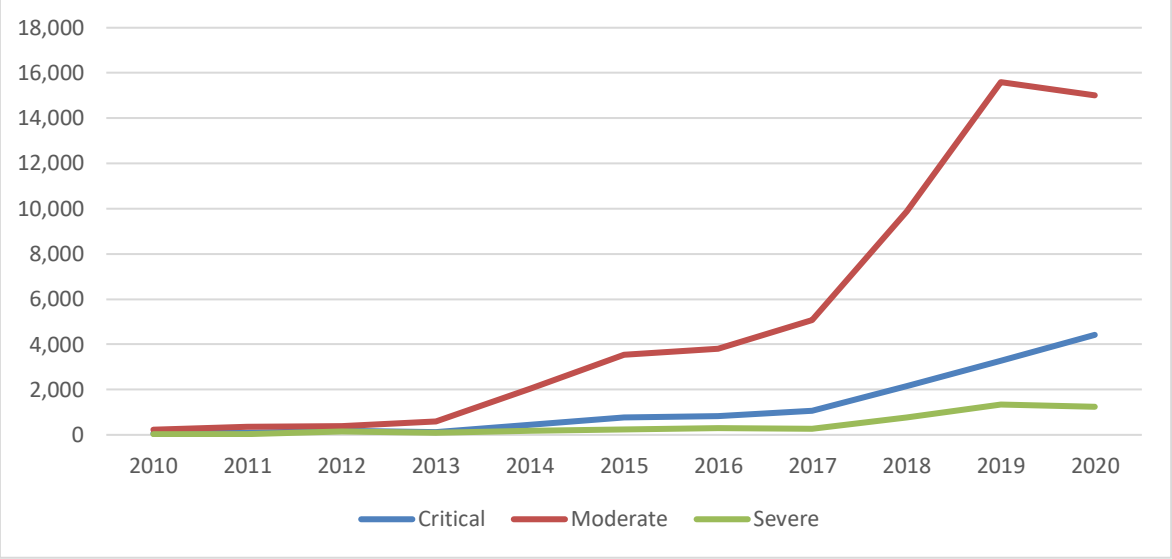
"Future-proofing pharmaceutical legislation: study on medicine shortages".[7] This analysis compares total remaining sales volume during a reported shortage to the sales volume for that same product a year earlier (reference period). This approach is based on several assumptions:

- The recorded sales in the year where the shortage was reported represent all remaining supply (i.e. all product sold is made available in the market and not held in stock, no safety stocks were used to mitigate the shortage)
- Demand can be approximated by the recorded sales exactly one year before the shortage was first reported (reference period).

We classify shortages according to their intensity. Severe shortages are those where volume dropped to 20% or less of the volume on the previous year, critical shortages are those where volume dropped to 21%-79% of the volume on year prior, and moderate when volume drops to 80% or more of the volume of the previous year. Figure SM-2 shows the evolution of the three types of shortages (i.e., critical, severe, moderate). The rise in the total number of shortages is driven by a significant growth in moderate shortages, however, since 2018 critical and severe shortages have been also on the rise.

Table SM-2 shows the proportion of products for which the volume decreased to 20% or less of the volume on the previous year. Such severe shortages were most commonly recorded in Romania (14% of all reported shortages) and Austria (13% of all reported shortages) during the period 2007-2021 (with the majority of data being recorded during 2017-2020).

Figure SM-2: Trend of volume drop for medicines in shortage (critical, severe, moderate)



Source: Technopolis Group, based on sales data from the IQVIA MIDAS database and shortage notifications by NCAs.

[7] https://data.europa.eu/doi/10.2875/211485

Table SM-2: Summary statistics on change in sales volumes for medicines in shortage, per country

Country	# Products	Median volume change (%)	Shortages with volume change to ≤ 20% (%)
Austria	144	-8%	13%
Croatia	88	-6%	8%
France	1,256	-3%	8%
Sweden	734	-2%	11%
Ireland	653	-2%	10%
Slovenia	674	-2%	9%
Estonia	566	-2%	8%
Italy	1,009	-2%	7%
Netherlands	1,417	-1%	8%
Spain	2,056	-1%	7%
Romania	7	1%	14%
Belgium	1,646	1%	9%
Norway	705	1%	8%
Portugal	2,823	1%	7%

Source: Technopolis Group, based on sales data from the IQVIA MIDAS database and shortage notifications by NCAs. Volume change calculated as the percentage change in between volume sold in first quarter of a shortage and volume 1 year prior

SM-3: Change of root cause reported for medicines

To better understand the circumstances that contribute to product shortages in their countries, National competent authorities (NCAs) may ask Marketing Authorisation Holder (MAHs) and wholesalers to submit information about the causes of the shortages along with the notification, and to indicate what steps are being taken to solve the issues. We use data from the study "Future-proofing pharmaceutical legislation : study on medicine shortages".8 Out of the 14 countries for which NCA representatives completed the study survey, eight indicate recording root causes in their reporting system (six according to their own definitions of root causes and two in line with SPOC definitions).9 In the data at our disposal, 15 out the 22 countries who reported shortage data have begun systematically collecting information on the causes of specific shortages.10 Some request this information using predefined categories of root causes. However, this has at times posed challenges when these categories are not sufficiently granular. For instance, in Sweden it was reported that, in a previous iteration of the reporting system, nearly all respondents selected 'other' as the root cause. Consequently, it was decided to expand the list of options, remove the 'other' category, and offer the possibility to add information in free form. Even when root causes are reported using a categorisation scheme, these schemes are not standardised between Member States, complicating sharing of information and comparative research. To improve this situation, in 2019 the SPOC network introduced a root causes classification scheme, comprising eight categories, which is used to recode root causes. [11]

[8] https://data.europa.eu/doi/10.2875/211485

[9] Belgium, Denmark, Germany, Ireland, the Netherlands and Portugal classify causes using their own definitions; Finland, Germany and Spain use classifications based on the SPOC definitions; Austria, Estonia, Latvia, Slovenia and Sweden do not record root causes.

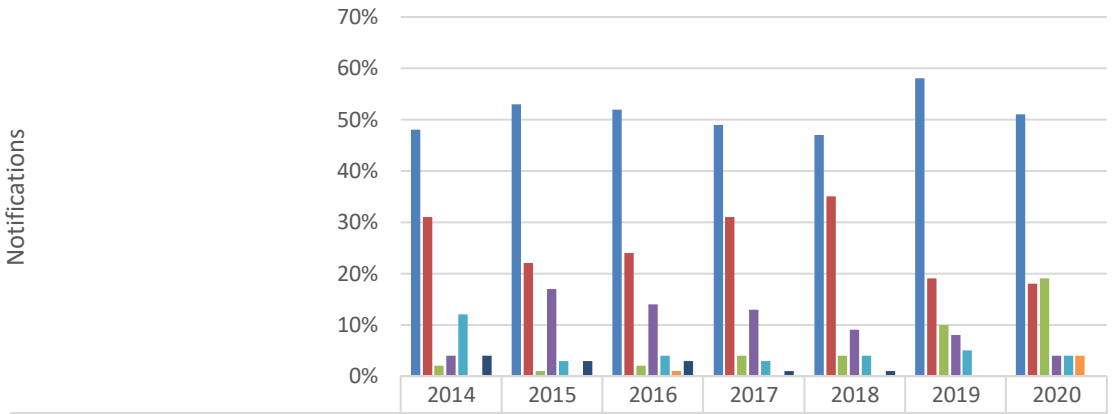
[10] These countries are Austria, Belgium, Croatia, Estonia, France, Hungary, Iceland, Ireland, Italy, Netherlands, Norway, Portugal, Romania, Spain and Sweden.

[11] HMA/EMA (22 January 2020).

A trend analysis of reported root causes by start year of notification shows that, between 2014 and 2020, (Figure SM-3):

- Quality & Manufacturing issues were consistently the main root cause of shortages, accounting for around half of all notifications; the relative contribution remained between 48% and 58% of all notifications.12
- Commercial reasons as a reported cause of shortages strongly increased between 2015 and 2018 up to a third (31%) of all notifications; this has since declined again to around a fifth (18-19%) of notifications.
- Unexpected increased demand strongly increased as a reported root cause in 2019 and 2020, becoming the second most reported reason (19%). For 2020, this includes the effects of COVID-19
- Distribution issues have steadily declined as a reported root cause of shortages since 2015.
- Regulatory issues have never been responsible for more than 5% of notifications (with a reported root cause) since 2015.
- Until 2019, unpredicted major events or natural disasters had been reported only sporadically as a root cause of shortages; however, 2020 saw a noticeable increase in reporting of this cause following the COVID-19 outbreak

Figure SM-3: Time trends in reported root causes of shortages (2014-2020)



	2014	2015	2016	2017	2018	2019	2020
Quality & Manufacturing issues	48%	53%	52%	49%	47%	58%	51%
Commercial reasons	31%	22%	24%	31%	35%	19%	18%
Unepected increased demand	2%	1%	2%	4%	4%	10%	19%
Distribution issues	4%	17%	14%	13%	9%	8%	4%
Regulatory issues	12%	3%	4%	3%	4%	5%	4%
Unpredicted major events or natural disasters	0%	0%	1%	0%	0%	0%	4%
Other issues	4%	3%	3%	1%	1%	0%	0%

Source: Technopolis Group, based on notifications in national shortage registries. Share expressed as the number of shortages reporting a particular root cause relative to all shortages with a reported root cause that year.

[12] All percentages reported as a share of all notifications for which a root cause was included in the reporting.

SM-4: Proportion of generic products in shortage

The study "Future-proofing pharmaceutical legislation: study on medicine shortages".[13] Found that shortages can arise for any type of medicine, but those at highest risk include pain relief medication, antihypertensives, anti-infectives and oncology medicines. Most shortages involve older, off-patent and generic medicines, which has been widely attributed to the low profit margins associated with these products. Just over half of all reported shortages (52%) involve generic medicines[14] while non-generic medicines account for 37% of reported shortages, with non-generic medicines including both still-patented medicines and original medicines that are not (or no longer) protected.

Table SM-4 shows the number of generic products in shortage by country. Portugal tops the list with 2558 products in shortage, followed by Czech Republic and Netherlands with 1602 and 1390 products in shortage, respectively.

Potentially an even more relevant distinction than that between generic and non-generic medicines is that between multisource and single source products. A multisource product can hereto be defined as a product for which there are multiple providers in a market offering an interchangeable product (based on equivalent active ingredient(s), strength and form). A recent White Paper by IQVIA finds that 52%-79% of shortages[15] involve generic products, which it assumes to be mainly 'multisource products'.[16] Additionally, it is estimated that 3.5% to 28%[17] of shortages involve 'no longer protected, original products' for which there are alternative generics or parallel import products available and that thus can be considered multisource products.

Table SM-4: Number of generic products in reported shortage per country

Country	Number of generic products in shortage
Portugal	2558
Czech Republic	1602
Netherlands	1390
Spain	1202
France	1156
Belgium	845
Slovenia	758
Italy	607
Slovakia	590

[13] https://data.europa.eu/doi/10.2875/211485

[14] Indicated in the IQVIA MIDAS data set as: generic product, early entry generic product or biocomparable product. Other categories not shown here are 'non categorized' and 'other' products.

[15] The unit of analysis used by IQVIA is the 'stock keeping unit' (SKU), used to normalize data across countries.

[16] Troein P, Newton M, Wasik AM, Coucoravas C, Scott K. (2020). Reporting of medicine shortages in Europe: white paper. IQVIA.

[17] The paper indicates that 5% to 40% of reported SKUs are 'no longer protected' original products and goes on to state that 70% of these have alternative generics or parallel import products. Thus, it can be said that 70% x (5% to 40%) = 3.5% to 28% of this group of products are multisource products.

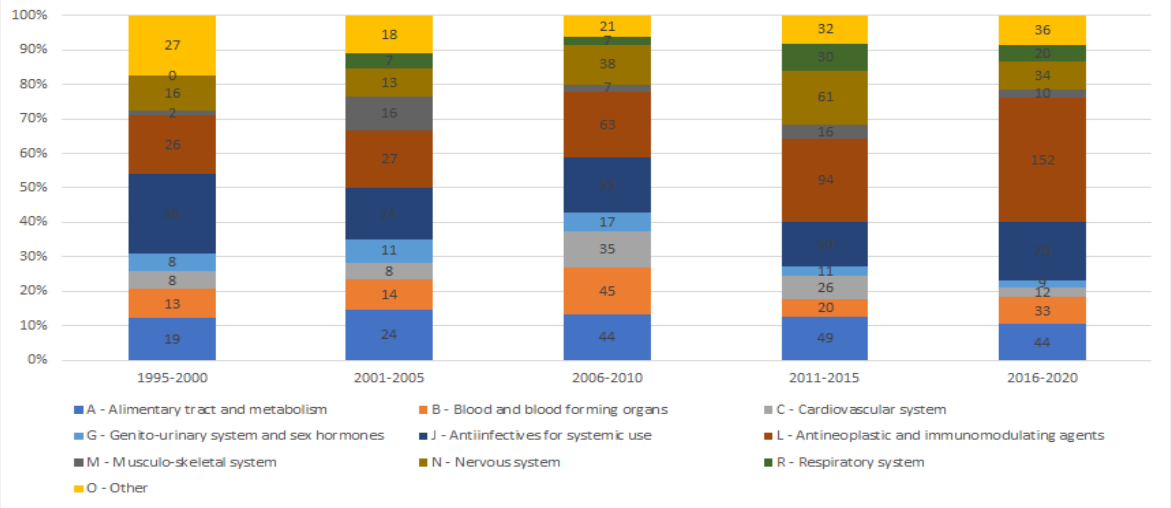
Finland	481
Estonia	476
Ireland	440
Sweden	305
Norway	259
Hungary	228
Romania	228
Germany	206
Austria	138
Croatia	72
Greece	17
UK	17
Latvia	5
Denmark	2
Iceland	2
Switzerland	1

Source: Technopolis Group, based on notifications in national shortage registries.

SM-5: Number of centrally authorised medicines per class, therapeutic area

To create an overview of the number of authorised medicines per therapeutic area we relied on level 1 ATC classification (main anatomical/pharmacological groups) of all products in the dataset in Figure SM-5.1.

Figure SM-5.1: Authorisations by EMA per ATC-L1 code per year



Source: Utrecht database.

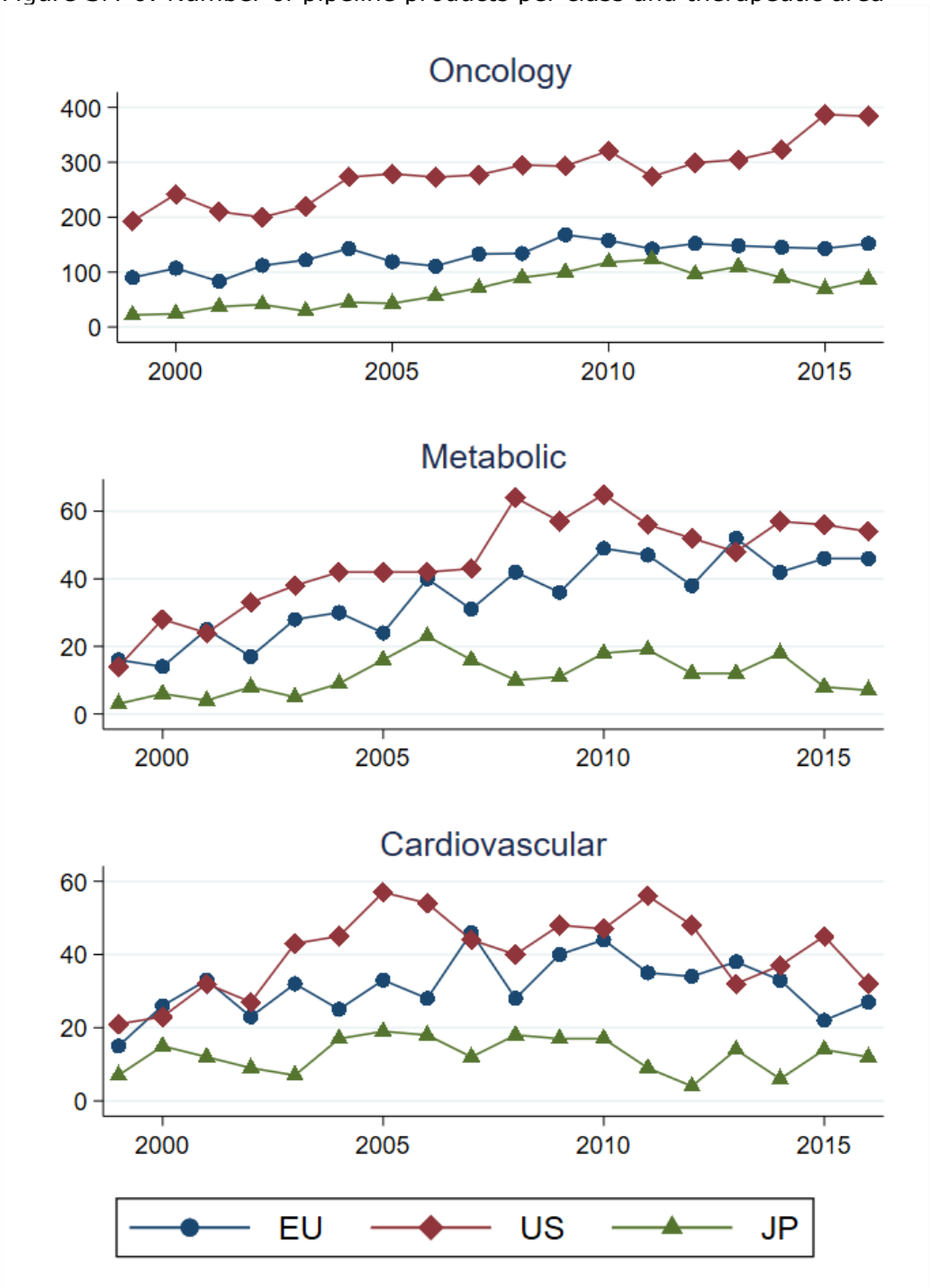
Over time, we see an increase in authorisation of antineoplastic and immunomodulating drugs.

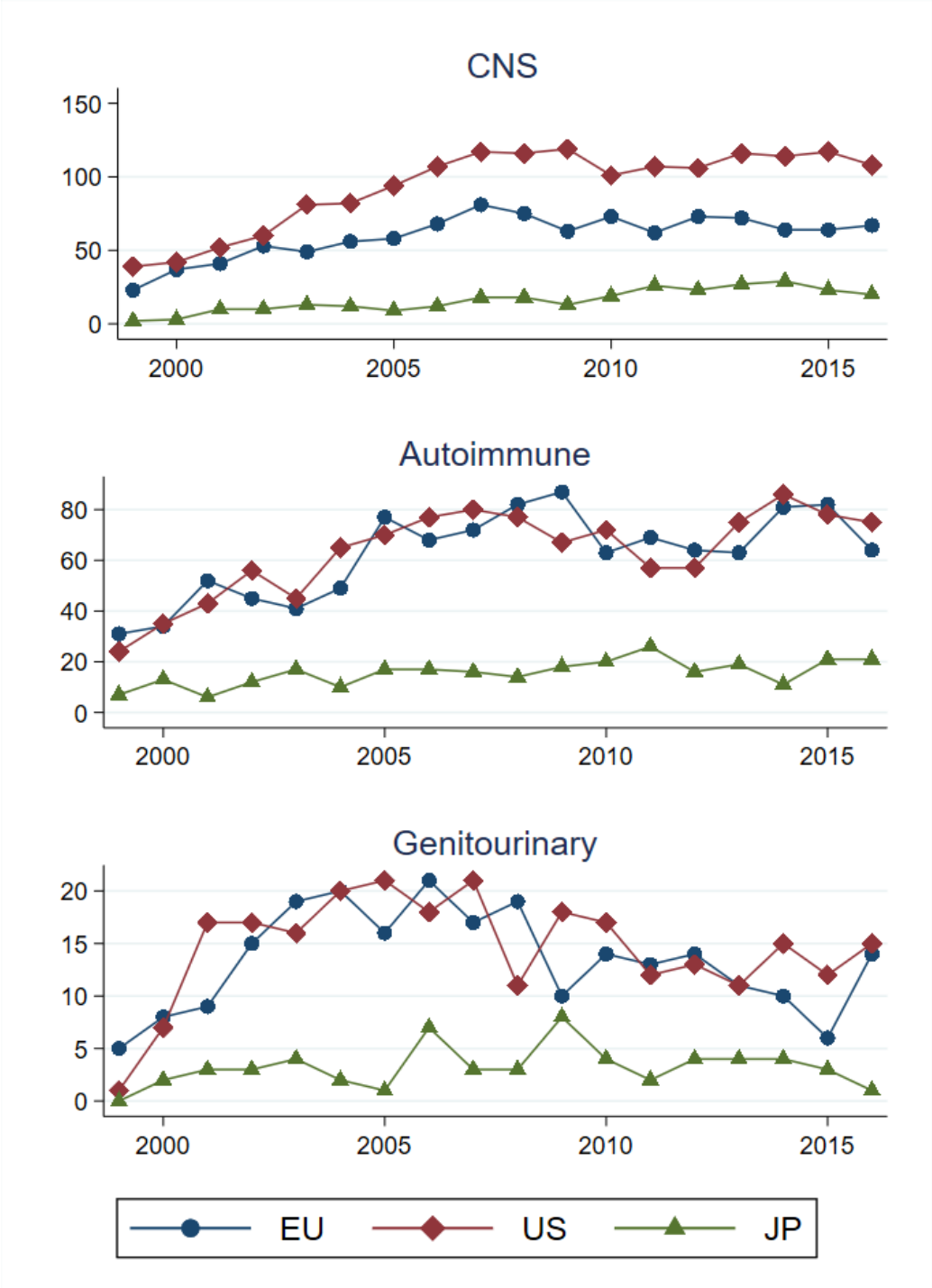
SM-6: Number of pipeline products per class and therapeutic area

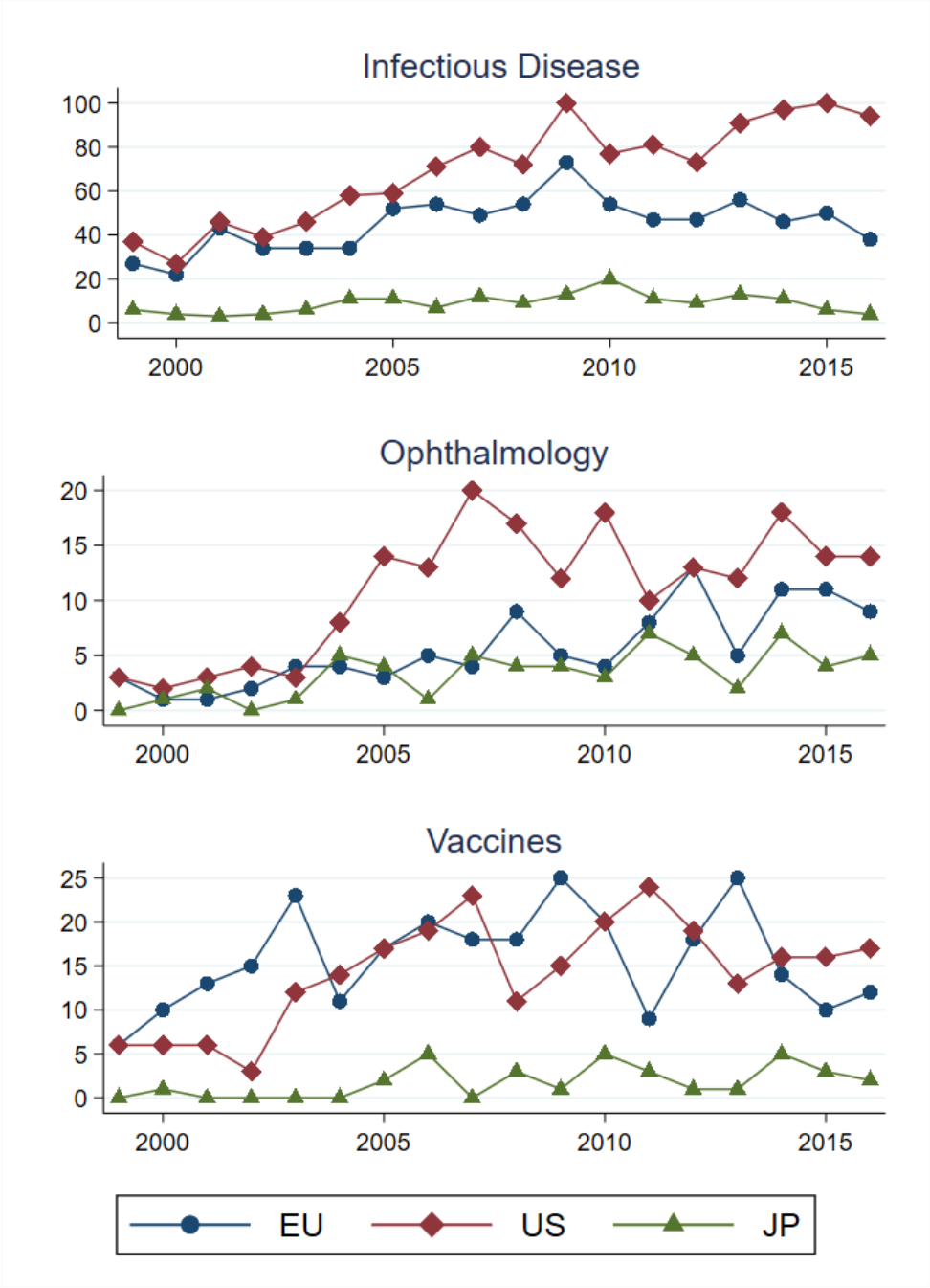
Indicator SM-6 is akin to RI-1 in that it shows the number of new candidate drugs per year; it differs from RI-1 in that it shows the new candidate drugs broken down by therapeutic area that they are being tested for.

We differentiate the same nine therapeutic areas as before: i) oncology, ii) metabolic/endocrinology, iii) cardiovascular, iv) CNS, v) autoimmune/inflammation, vi) genitourinary, vii) infectious diseases, viii) ophthalmology, and ix) vaccines.

Figure SM-6: Number of pipeline products per class and therapeutic area




CNS
150
100
50
0
2000
2005
2010
2015
Autoimmune
80
60
40
20
0
2000
2005
2010
2015
Genitourinary
20
15
10
5
0
2000
2005
2010
2015
EU
US
JP


Infectious Disease
100
80
60
40
20
0
2000
2005
2010
2015
Ophthalmology
20
15
10
5
0
2000
2005
2010
2015
Vaccines
25
20
15
10
5
0
2000
2005
2010
2015
EU
US
JP

1.6 EFFICIENCY INDICATORS

Indicator name	Indicator description
EFF-1	Time from start of Phase1 to completion of Phase 3 clinical trials
EFF-2	Number of EMA approvals by year
EFF-3	EMA assessment times including accelerated assessments

EFF-1: Time from start of Phase 1 to completion of Phase 3 clinical trials

Indicator definition and relevance with respect to the evaluation

Efficiency indicator 1 is a measure of the time spent in each development phase for medicinal products on average across the same four analysis regions/countries used for IEC-1-4 and IEC-6 and RI-1-6. However, for EFF-1, instead of assessing the productivity or innovation of each region, it is changes in efficiency in terms of the average length of time that medicinal products spend in different phases of clinical development that is assessed. Therefore, the aim was to observe if the EU demonstrated changes in efficiency following the implementation of the general pharmaceutical legislation, or if the USA, Japan, or Switzerland demonstrated changes in efficiency during the same period but of course without being influenced by the implementation of the general pharmaceutical legislation.

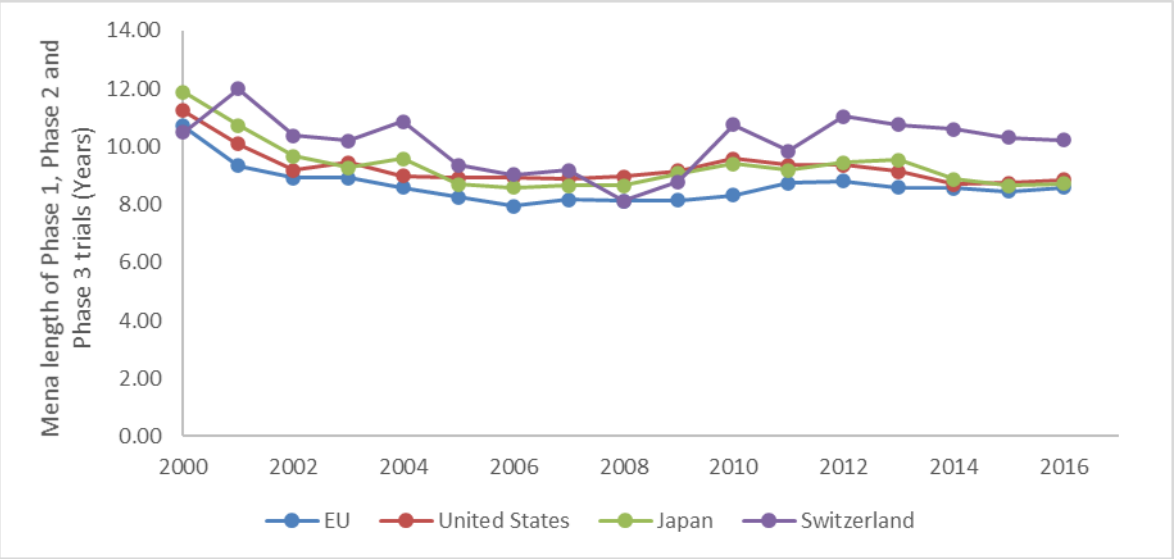
Methodology

The base dataset for EFF-1 is the same as that used for IEC-6 and IEC-9 and consists of over 172,000 Phase 1, Phase 2, and Phase 3 clinical trials contained in Trialtrove with start dates between 2000 and 2020. Each trial was assigned a development phase and an analysis region (USA, EU, Japan, or Switzerland) based on the information contained in Trialtrove. In addition, only trials with known start dates and known or anticipated end dates were included. The countries in what was the EU28 were treated as always having been in the EU for the entire period of the analysis (2000-2020). The clinical trials included in the mean length of trial calculations do not take into account the number of patients recruited in each region or country (such data are not available), so a trial with a least one site and therefore one or more patients per region or country is of necessity counted for that region or country. So as to not unduly bias the data, the mean length of trial calculations were cut off at 2017, as many trials in later years are those that were terminated early, thus making the average length of the trials appear shorter than in reality. Furthermore, any trials recorded as being terminated due to business or other nonclinical reasons (i.e., not related to either the safety or the efficacy of the medicinal product under investigation) were also excluded. Trials conducted in multiple regions or countries were included, as later phase trials are almost exclusively run globally or in at least two or more of the seven major pharmaceutical markets. The mean number of clinical trials starting each year in each phase in each analysis region or country and standard deviations were determined for both the pre and post periods. As with IEC-1-4, Shapiro-Wilk tests were conducted to check data distribution prior to

parametric (Welch's t-test) or non-parametric (Mann Whitney U test) tests for significance between the pre and post groups.

EFF-1 investigated the total length of time taken for products to begin Phase 1 and end Phase 3 with trials starting in each year in each of the markets under investigation, namely the EU, the USA, Japan, and Switzerland, in time periods both pre and post the implementation of the 2004 revision of the general pharmaceutical legislation. Top level results comparing each analysis region or country are shown in Figure EFF-1 and Table EFF-1. In all analysis regions, no significant difference was observed between the pre and post periods.

Figure EFF-1 Total mean length of Phase 1, Phase 2, and Phase 3 trials conducted in the EU, the USA, Japan, and Switzerland by start year, 2000-2017.



Source Trialtrove (2000-2017).

Table EFF-1 Descriptive statistics for the total mean length of Phase 1, Phase 2, and Phase 3 trials conducted in the EU, the USA, Japan, and Switzerland

Analysis region	Pre or post	MEAN (years)	STDEV	LOW	HIGH	N number	MANN-WHITNEY U TEST (P-value)
EU	Pre	9.29	0.75	8.55	10.04	3,159	**0.078**
EU	Post	8.49	0.25	8.24	8.74	10,699	
USA	Pre	9.79	0.81	8.97	10.60	3,983	**0.135**
USA	Post	9.10	0.32	8.77	9.42	14,431	
Japan	Pre	10.23	0.96	9.27	11.19	388	**0.064**
Japan	Post	9.06	0.33	8.73	9.39	3,615	
Switzerland	Pre	10.78	0.64	10.14	11.43	400	**0.092**
Switzerland	Post	9.96	0.89	9.07	10.85	1,154	

Source: Trialtrove. Mean total length of Phase 1, Phase 2, and Phase 3 trials starting each year in each analysis region and country, and standard deviations, were determined for both the pre and post periods. Shapiro-Wilk tests were conducted to check data distribution prior to non-parametric (Mann-Whitney U test) tests for significance between the pre and post groups. Significant differences between the pre and post periods are highlighted in bold.

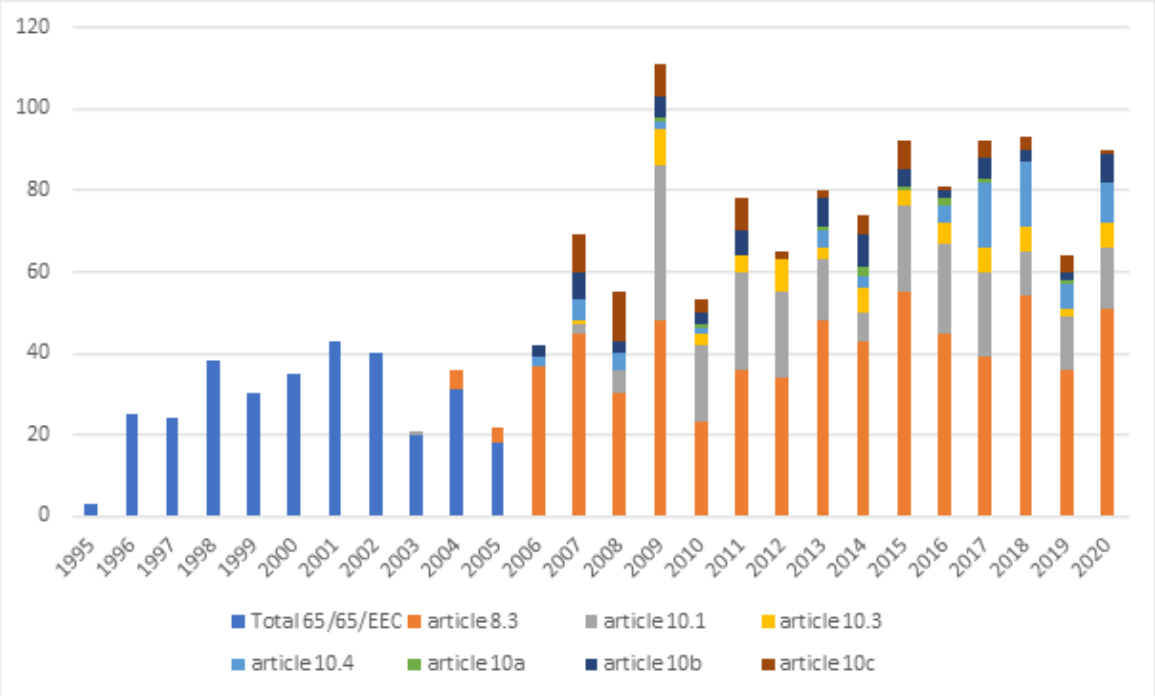
Interpretation of possible causes for changes in EFF-1

EFF-1 demonstrates that the EU has not lost any efficiency compared with other jurisdictions in terms of the overall length of time taken for products to transition from Phase 1 to Phase 3 as a result of the implementation of the general pharmaceutical legislation, although the same trend was observed for all analysis regions or countries. So, while attrition rates and overall difficulty in drug development have been seen to increase in the past 20 years, in terms of the overall length of trials, with the caveats explained above regarding the trials included, the implementation of the general pharmaceutical legislation does not seem to have had a significant effect on the overall length of time taken for products to progress from Phase 1 to Phase 3.

EFF-2: Number of EMA approvals by year

In Figure EFF-2.1 the number of medicinal product authorisations as reported in ACC-1 is stratified by legal bases. The Figure confirms an increase in the number of approvals by year, including a small upward trend in the number of authorisations based on a complete dossier (article 8(3)) as well as an increase in the number of similar biological applications (article 10(4)).

Figure EFF-2.1: Number of EMA approvals by legal basis (yearly, 1995-2020)



Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

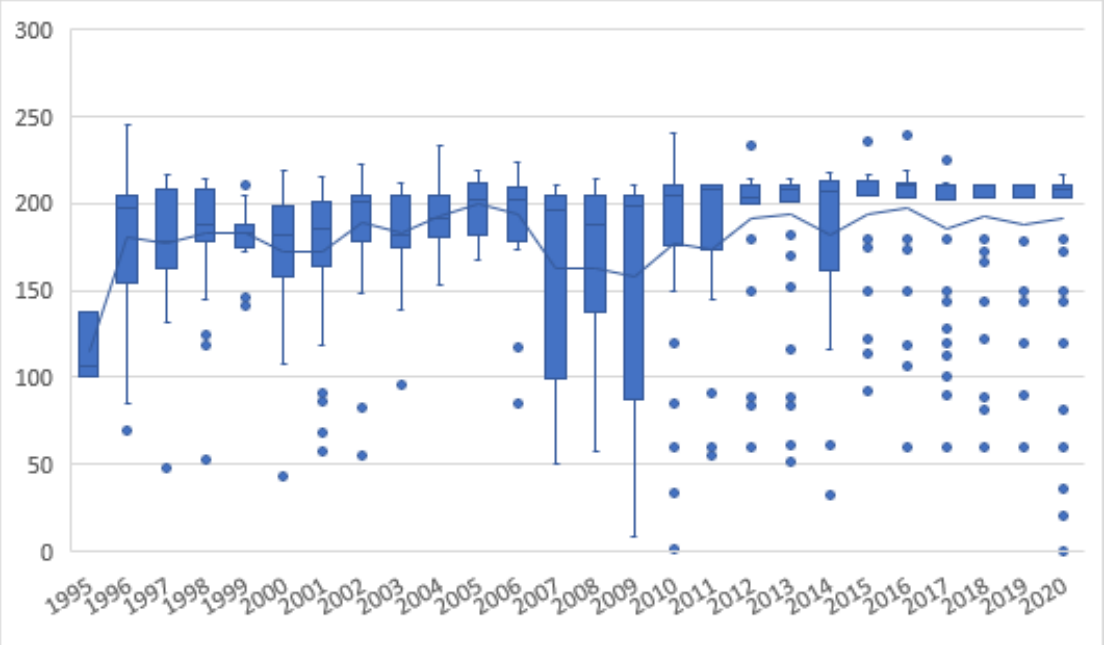
EFF-3: EMA assessment times including accelerated assessments

Figures EFF-3.1 and EFF-3.2 provide a detailed picture of EMA assessment times by year by distinguishing between active time (Figure EFF-3.1) and clock-stop time (Figure EFF-3.2). Moreover, Regulation (EC) No 726/2004 allowed for accelerated assessment of certain marketing authorisation applications. Figure EFF-3.3 provides an overview of the number of accelerated assessments that were granted by CHMP at the start of the marketing authorisation procedure as well as the number of assessments that were executed with accelerated timelines.

Figure EFF-3.4 compares executed accelerated assessments by EMA with executed priority reviews by the FDA, focusing on the subset of matched NASs/NMEs. A Priority

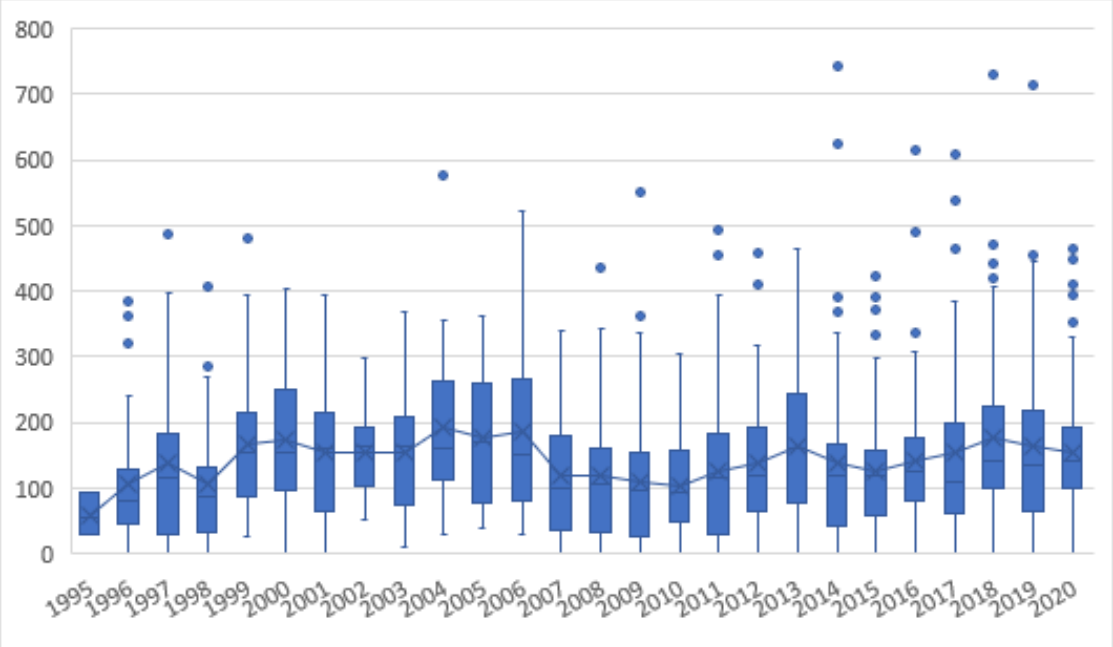
Review designation means FDA's goal is to take action on an application within 6 months. Accelerated Assessment permits a reduction in active assessment time from 210 to 150 days.

Figure EFF-3.1: Active assessment times for EMA authorised medicines (yearly, 1995-2020)



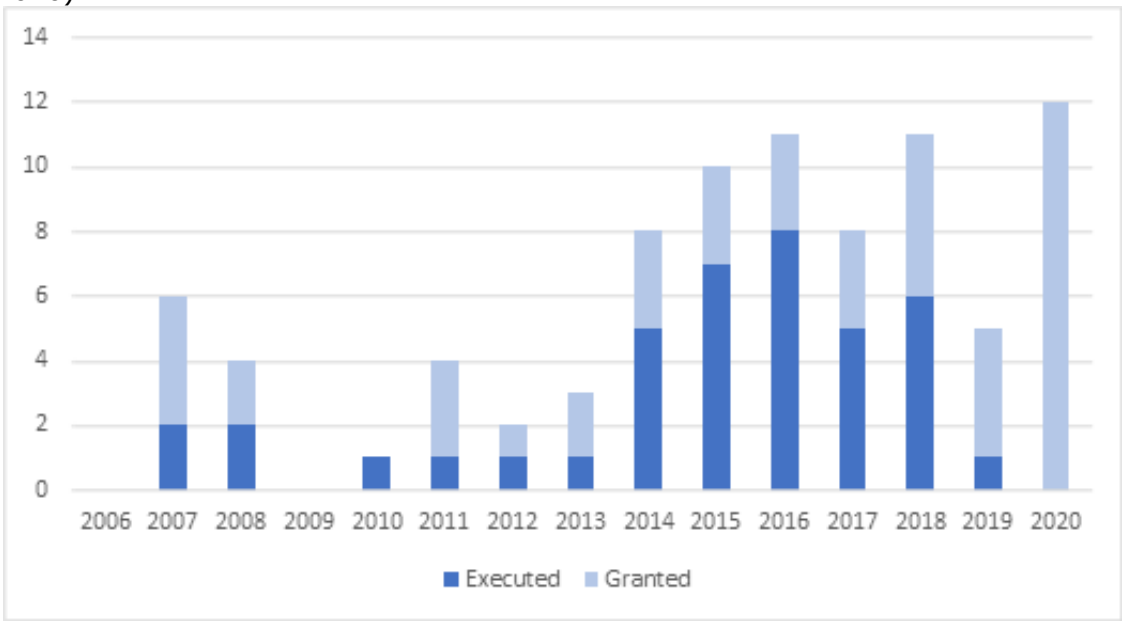
Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

Figure EFF-3.2: Clock-stop assessment times for EMA authorised medicines (yearly, 1995-2020)



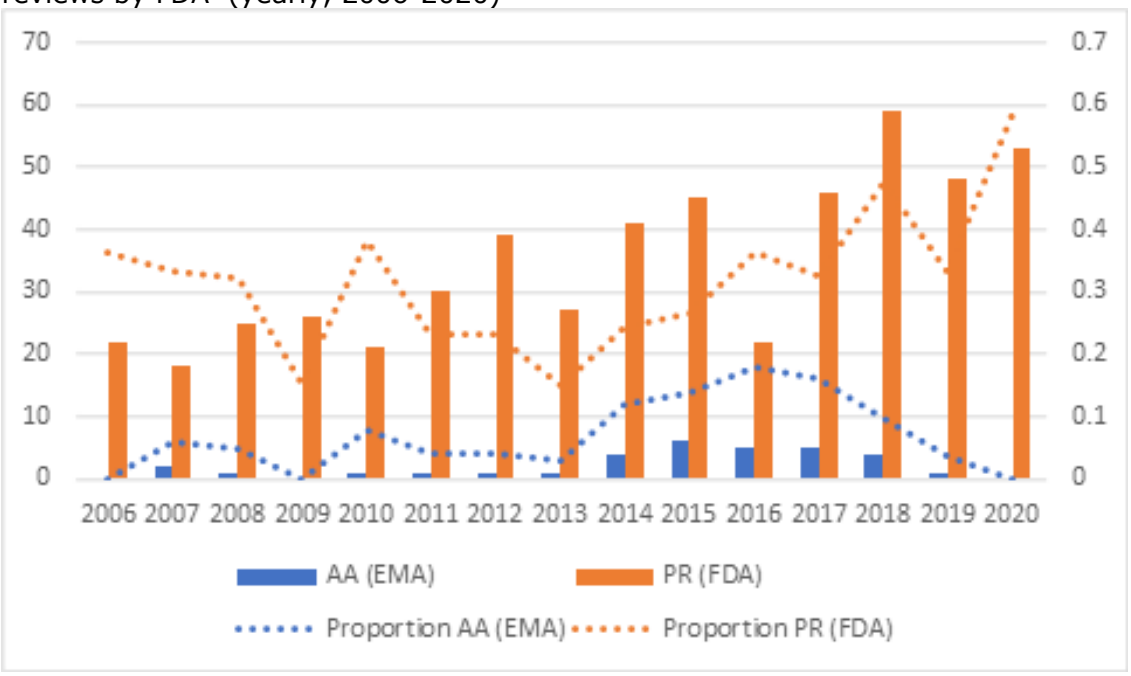
Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

Figure EFF-3.3: Executed and granted accelerated assessments by EMA (yearly, 2006-2020)



Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

Figure EFF-3.4: Number and proportion of accelerated assessments by EMA and priority reviews by FDA (yearly, 2006-2020)



Source: Database maintained by Utrecht University based on public data from EMA, European Commission and FDA.

It is found that:

- There is no clearly discernible trend is visible in active assessment time and clock stop time at EMA
- The number of granted accelerated assessments is increasing over time
- The number of executed accelerated assessments increases up to 2018, but has been relatively low in 2019-2020
- The number and proportion of accelerated assessments executed by EMA is relatively low compared to the number of priority reviews executed by FDA.

1.7 MANUFACTURING INDICATORS

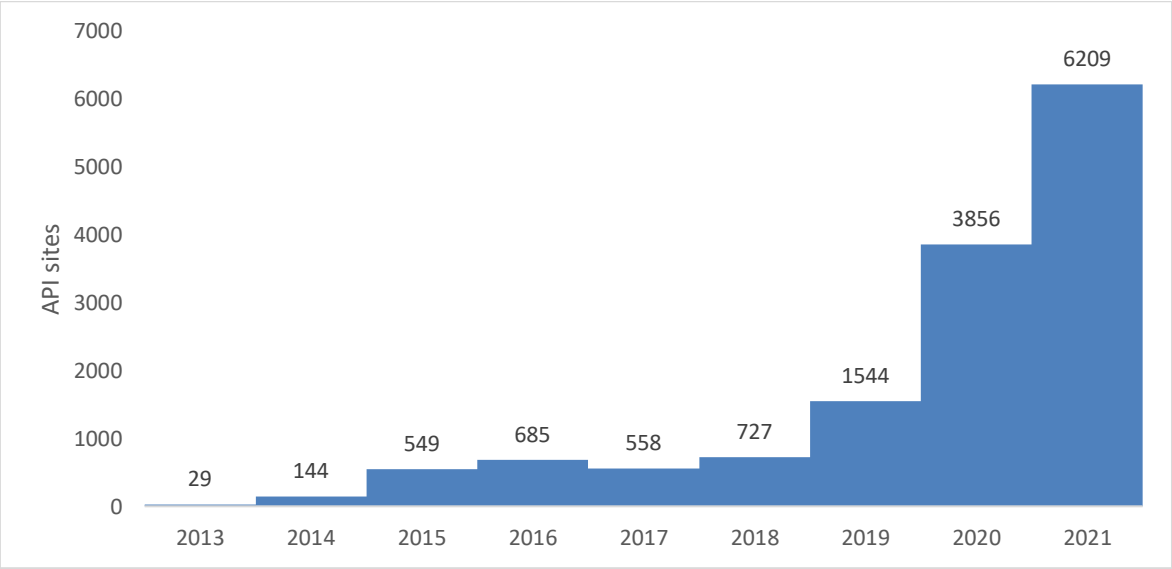
Indicator name	Indicator description
MI-1	Number of third-country API sites, stratified by geography
MI-2	Number of EU-registered API sites, stratified by MS
MI-3	Number of non-compliance of GMP, stratified by countries

MI-1: Number of third-country API sites, stratified by geography

The community format for the API registration certificate was established in accordance with art. 47 of directive 2004/27/EC and art. 51 of directive 2004/28/EC, amending directives 2001/83/ec and 2001/82/EC respectively. For the manufacturing indicators in this section we use the EudraGMDP database, which is the Community database on manufacturing, import and wholesale-distribution authorisations, and good manufacturing (GMP) and good-distribution-practice (GDP) certificates. A public version of the database has been available since 2011.

As shown in Figure MI-1, the number of third country registered API sites remained somewhat stable in 2015-2018 (averaging 630 sites per year). However, since 2019 this number has almost doubled every year. By 2021, there were 6209 API sites registered in third countries (with links to companies with a main site registered in the EU).

Figure MI-1: Number of third country registered API sites

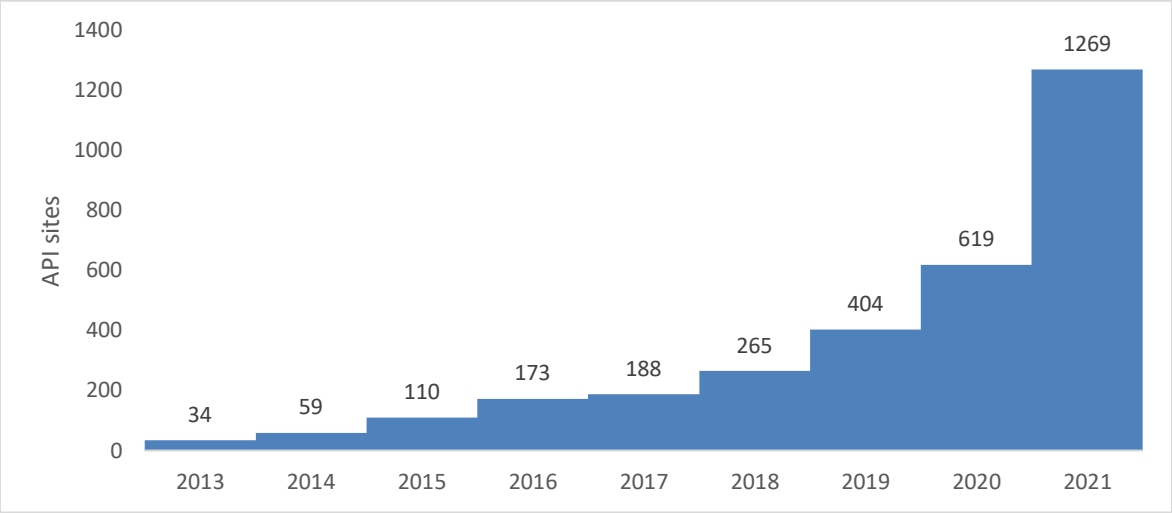


Source: EudraGMDP. This figure is based on information reported by 23 EU countries and the UK. Denmark, Estonia, Luxemburg and Romania are excluded.

MI-2: Number of EU-registered API sites

On the other hand, the number of API sites registered in the EU has seen a steady growth since 2013, although it almost doubled in 2021 when there were 1269 registered API sites (Figure MI-2).

Figure MI-2: Number of EU-registered API sites

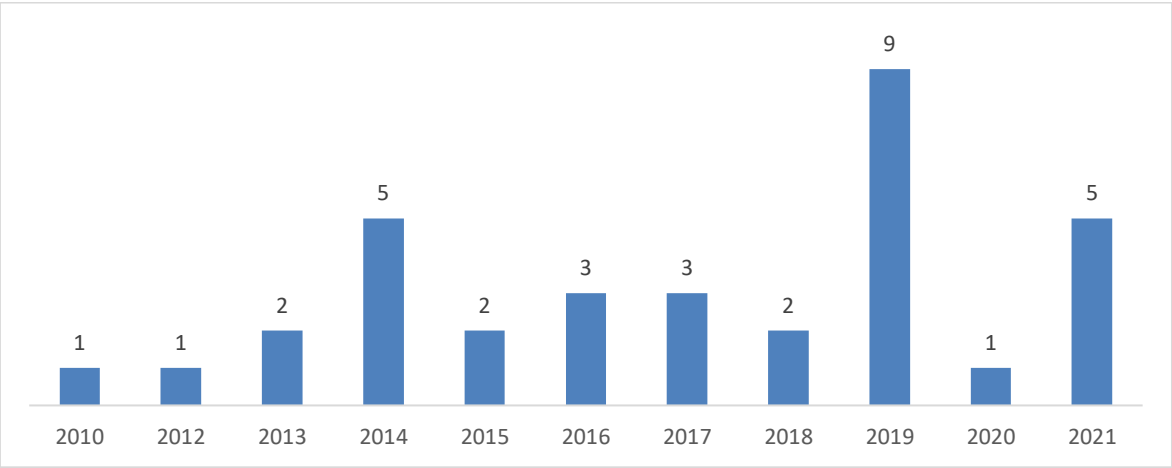


Source: EudraGMDP. This graph presents information for 26 EU countries and the UK. Romania is excluded.

MI-3: Number of non-compliance of GMP, stratified by countries

The General Pharmaceutical Legislation aimed to harmonise Good Manufacturing Practices (GMP) across the EU. To this end, a Community format for GMP Certificate was established in accordance with Art. 47 of Directive 2004/27/EC and Art. 51 of Directive 2004/28/EC, amending Directives 2001/83/EC and 2001/82/EC respectively. Only few EU counties report non-compliance of GMP, among them Austria, Czechia, Denmark, Spain, France, Hungary, Italy, Netherlands and Romania. There is no clear pattern in the number of non-compliance reports per year, however, as shown in Figure MI-3, more of these reports were issued in 2014, 2019 and 2021.

Figure MI-3: Number of non-compliance of GMP reports



Source: EudraGMDP. This graph presents the number of non-compliance of Good Manufacturing Practice reports reported by 9 EU countries and the UK. The 9 EU countries include Austria, Czechia, Denmark, Spain, France, Hungary, Italy, Netherlands and Romania. Date of data retrieval: October 28, 2021.

1.8 INDICATORS SPECIFIC TO ANTIMICROBIAL RESISTANCE

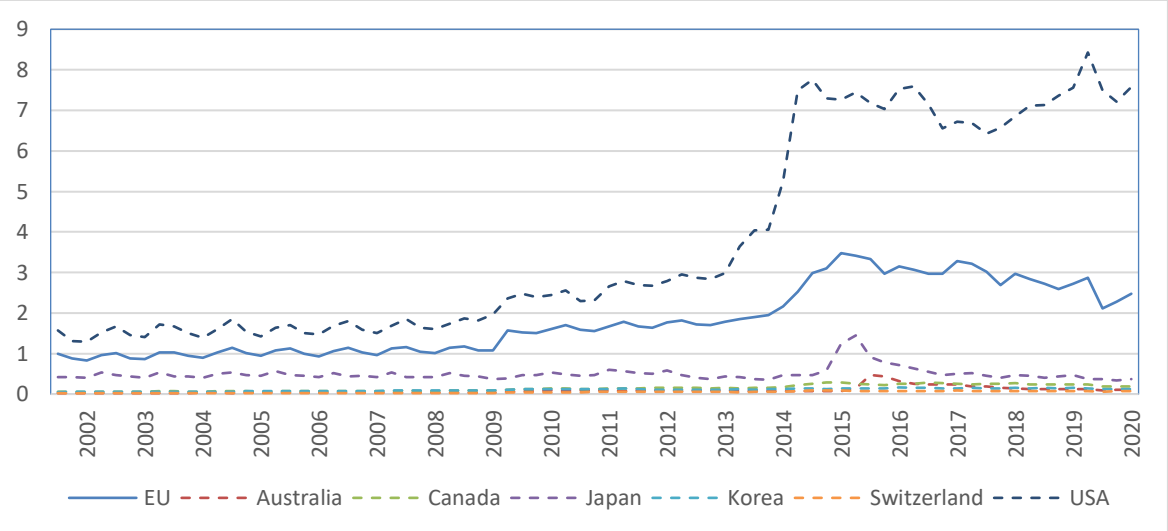
Indicator name	Indicator description
AMR-1	Sales volume of antibiotics
AMR-2	Number of antibiotics withdrawn from EU markets*
AMR-3	Number of antibiotics approved per year
AMR-4	Number of antibiotic medicine candidates in the R&D pipelines

* Note that this indicator was not calculated

AMR-1: Sales volume of antibiotics

To construct AMR-1, we use the IQVIA-MIDAS dataset (see the 'Affordability and Single Market Indicators' section for a detailed description of the data and caveats). We add up all drug sales falling into the ATC categories J01 (antibiotics), but also J02 (antifungals), J03 (antimycobacterials) and J05 (antivirals). Figure AMR-1.1 reports the resulting time series. Total sales of antibiotics in the EU have slowly increased from 2002 to 2014, then rapidly risen until 2016 and have since declined again. The US display a similar pattern of even more rapidly rising antibiotics expenses in 2014 which have since stabilized at a high level. Most other comparators, except Japan, are dwarfed by the total sales of antibiotics in the US and the EU.

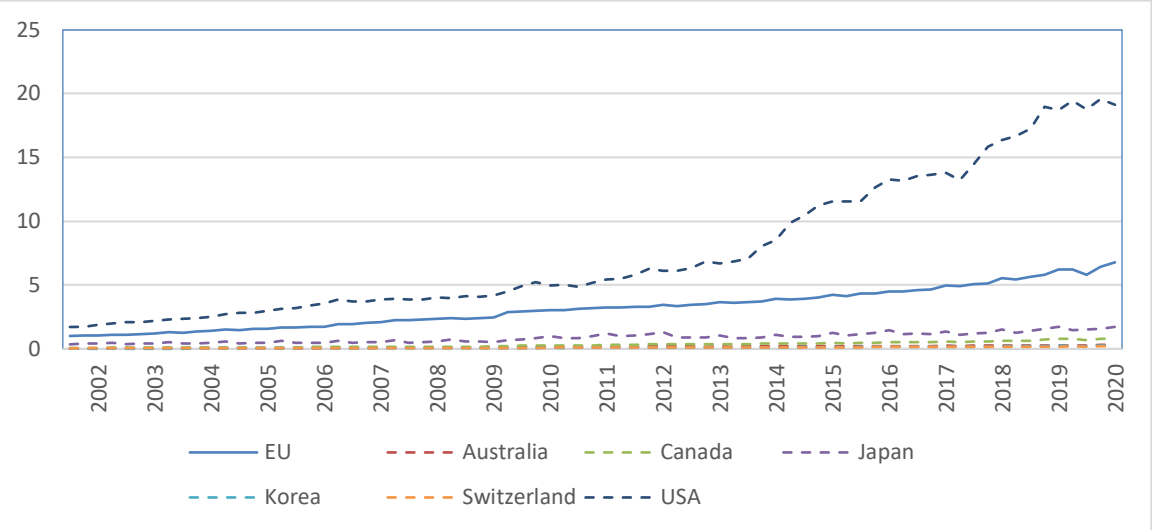
Figure AMR-1.1: Total sales of antibiotics



Source: IQVIA-MIDAS

Figure AMR-1.2 presents total sales by region for biological drugs. Sales of biological drugs in the EU have steadily increased in the EU and are now at more than six times their 2002 level. The increase in the sales of biological drugs is even more pronounced in the US. Again, other comparators – except Japan – are relatively small compared to the US and the EU.

Figure AMR-1.2: Total sales of biological drugs



Source: IQVIA-MIDAS

AMR-3-4: Indicator definition and relevance with respect to the evaluation

Antimicrobial resistance is one of the most significant healthcare challenges of the next decade or sooner, and there is a very real possibility that humanity will truly enter a post antibiotic era where, for example, currently routine lifesaving procedures become very high risk due to the possibility of secondary infection. Despite this, it has been over 30 years since a new class of antibiotic was discovered and brought to market, and the economics to drive such discovery are at odds with worldwide drug discovery driven by private business. Any new antibiotic, even if discovered and brought to market, is, by necessity, usually reserved as a last line treatment and only prescribed carefully and rarely to treat infections shown to be resistant to all other classes of antibiotic. This means that the economics of developing a new antibiotic are heavily stacked against profit driven development. Therefore, legislation and the related financial incentives that any legislation might facilitate are likely to be required to promote development of new antibiotics. It is the intention of AMR-3 and 4 to assess the relative productivity of various regions and countries with respect to the development of antimicrobial products, in terms of final output as measured by approved antimicrobials (AMR-3), and overall productivity of clinical research as measured by the number of clinical trials and products in the development pipeline (AMR-4).

Methodology – AMR-3 and AMR-4

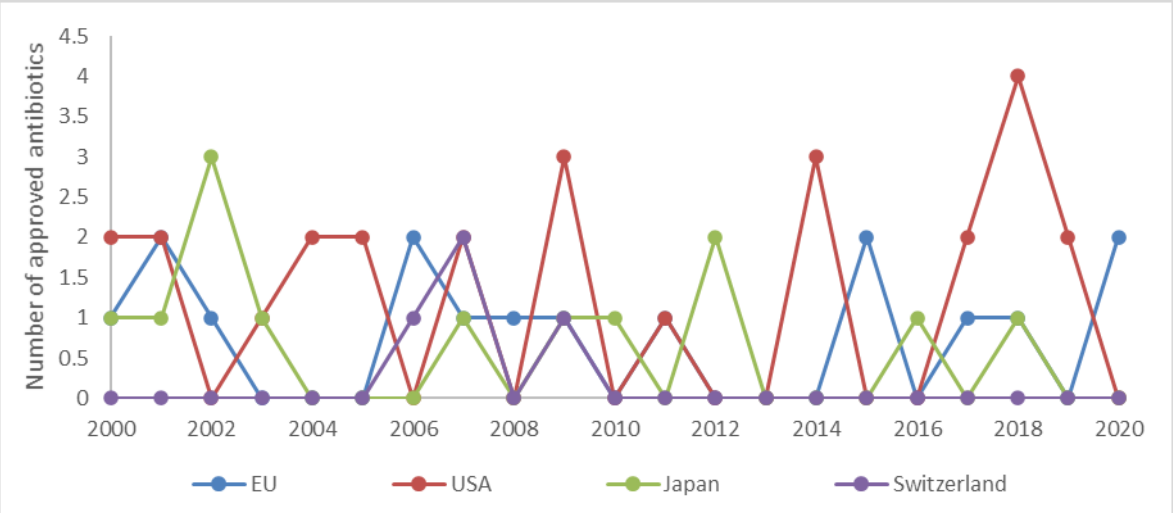
Throughout, all drug approval data are based on that contained in Pharmaprojects and Biomedtracker as of August 2021. The base dataset for AMR-3 contained 4,981 products with a known approval date anywhere in the world. The approval year was set as first approval only; the number and dates of subsequent approvals relating to indication expansion were not counted. Therefore, in the case of approvals in the EU, no distinction is or can be made between drugs approved via the centralised or decentralised procedures using data from Pharmaprojects. Furthermore, all member states currently in the EU plus the UK were treated as always having been part of the EU for the entire analysis period. The scope of Pharmaprojects is also limited in that while the majority of medicinal products in development are covered, including biosimilars and reformulations relating to fixed dose combinations and route of administration reformulations by originator companies, approvals of generics or drug combinations are not recorded. Antibiotic products were selected based on recorded

therapeutic class. Distinctions were not made between novel classes of antibiotics and existing classes, but reformulations of existing antibiotics were excluded. Pre or post refers to the analysis period before (pre defined as 2000-2004) or after (post defined as 2007-2020) the implementation of the general pharmaceutical legislation. Mean approvals per year and standard deviations were calculated for both the pre and post periods. For all analyses, if the number of observations (number of approved products or clinical trials) was less than 30, no statistical testing was performed or reported. For AMR-4, the clinical trial dataset used for previous indicators was curated to extract those trials for known antimicrobials as found using the criteria outlined above for AMR-3 for approved products and for those in the pipeline. Both the number of trials starting each year and the number of antimicrobial compounds in trials were counted for each year and each analysis region. As with AMR-3, n numbers were not sufficient for statistical analysis.

AMR-3: Number of antibiotics approved per year

AMR-3 investigated approvals of antibiotic medicines in the EU, the USA, Japan, and Switzerland in time periods both pre and post the implementation of the 2004 revision of the general pharmaceutical legislation. Top level results comparing the four analysis regions for all antibiotic products, not including reformulations, are shown in Figure AMR-3 and Table AMR-3. Reformulations are excluded as they are not expected to contribute to preventing the continued rise of AMR. In keeping with known trends, in the EU, the USA, and Japan, the mean number of antibiotics approved was shown to decrease in the post period vs the pre period, but n numbers were not sufficient for statistical analysis. In Switzerland, the average number of antibiotics was shown to increase in the post period vs the pre period, but, again, n numbers were not sufficient for statistical analysis.

Figure AMR-3 Number of approved antibiotics by year in the EU, the USA, Japan, and Switzerland.



Source: Pharmaprojects 2000-2020.

Table AMR-3 Descriptive statistics for the number of antibiotics approved in the EU, the USA, Japan, and Switzerland (excluding reformulations)

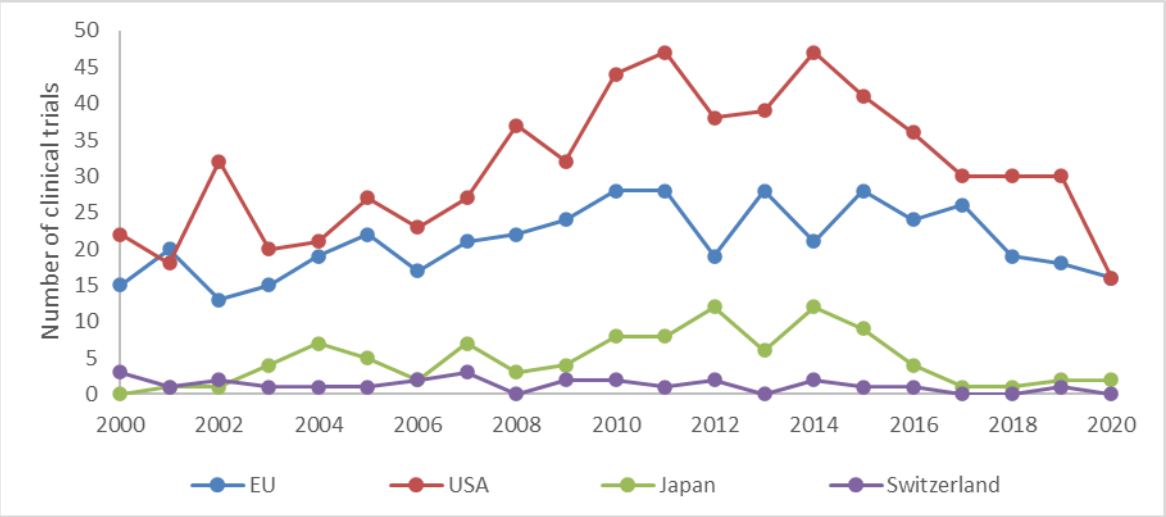
Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH
EU	Pre	0.80	0.75	0.05	1.55
EU	Post	0.71	0.70	0.01	1.41
USA	Pre	1.40	0.80	0.60	2.20
USA	Post	1.21	1.37	-0.16	2.59
Japan	Pre	1.20	0.98	0.22	2.18
Japan	Post	0.50	0.63	-0.13	1.13
Switzerland	Pre	0.00	0.00	0.00	0.00
Switzerland	Post	0.21	0.56	-0.34	0.77

Source: Pharmaprojects (2021) and Biomedtracker (2021). Antibiotic products were selected based on recorded therapeutic class. Distinctions were not made between novel classes of antibiotics and existing classes, but reformulations of existing antibiotics were excluded. Mean approvals per year and standard deviations were calculated for both the pre and post periods.

AMR-4: Number of antibiotic medicine candidates in the R&D pipeline

AMR-4 investigated the number of antibiotic medicine candidates in the R&D pipeline in the EU, the USA, Japan, and Switzerland in time periods both pre and post the implementation of the 2004 revision of the general pharmaceutical legislation. Top level results comparing the number of trials starting each year in the four analysis regions for all antibiotic products, not including reformulations, are shown in Figure AMR-4.1 and Table AMR-4.1. The number of products in the R&D pipeline with trials starting in each year in each analysis region are shown in Figure AMR-4.2 and Table AMR-4.2. As with AMR-3, reformulations were excluded, as they are not expected to contribute to preventing the continued rise of AMR. In the EU and the USA, more trials for antibiotics were found to start on average in each year in the post period compared to the pre period. The tailing off of trial numbers in the US towards the end of the time period may be attributable to what is often perceived as the failure of Generating Antibiotic Incentives Now (GAIN), which was passed in 2012 as part of the Food and Drug Administration Safety and Innovation Act (FDASIA). While GAIN may have stimulated some trial activity in the early period from 2012, the failure to target Qualified Infectious Disease Product (QIDP) criteria tightly enough to match unmet need may have led to the subsequent fall in trial numbers. The number of trials starting in each year was shown to increase in Japan and decrease in Switzerland, but the n numbers were not sufficient for statistical analysis. The number of products in the R&D pipeline in each year increased in the EU, the USA, and Switzerland in the post period compared to the pre period. In Japan, the number of products also increased in the post period, but the n number was not sufficient for statistical analysis.

Figure AMR-4.1 Number of clinical trials for antibiotics starting in each year in the EU, the USA, Japan, and Switzerland.



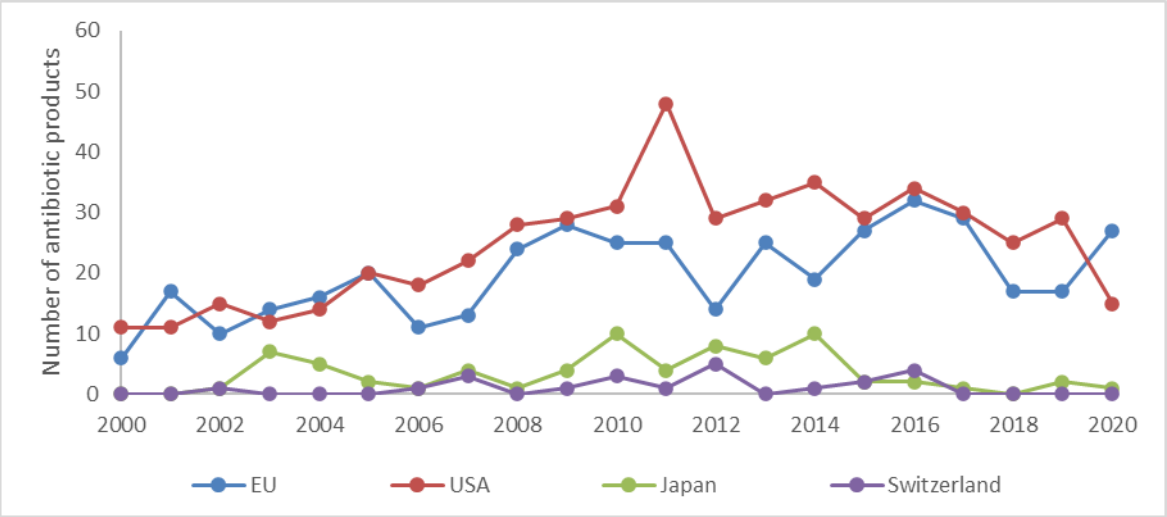
Source: Trialtrove 2000-2020.

Table AMR-4.1 Descriptive statistics for the number of clinical trials for antibiotics in the EU, the USA, Japan, and Switzerland (excluding reformulations)

Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH
EU	Pre	16.40	2.65	13.75	19.05
EU	Post	23.00	4.02	18.98	27.02
USA	Pre	22.60	4.88	17.72	27.48
USA	Post	35.29	8.21	27.08	43.49
Japan	Pre	2.60	2.58	0.02	5.18
Japan	Post	5.64	3.66	1.99	9.30
Switzerland	Pre	1.60	0.80	0.80	2.40
Switzerland	Post	1.07	0.96	0.11	2.03

Source: Pharmaprojects (2021) and Trialtrove (2021). Antibiotic products were selected based on recorded therapeutic class. Distinctions were not made between novel classes of antibiotics and existing classes, but reformulations of existing antibiotics were excluded. Data were not split by phase to preserve the n number for the number of trials in Japan and Switzerland. Mean approvals per year and standard deviations were calculated for both the pre and post periods.

Figure AMR-4.2 Number of antibiotic products with clinical trials starting in each year in the EU, the USA, Japan, and Switzerland.



Source: Trialtrove 2000-2020.

Table AMR-4.2 Descriptive statistics for the number of antibiotics in the R&D pipeline in the EU, the USA, Japan, and Switzerland (excluding reformulations)

Region of approval	Pre or post	MEAN	STDEV	LOW	HIGH	WELCH'S T-TEST (P-value)
EU	Pre	11.75	4.15	7.60	15.90	**0.012**
EU	Post	21.86	6.36	15.50	28.21	
USA	Pre	12.25	1.64	10.61	13.89	**0.001**
USA	Post	29.93	6.61	23.32	36.53	
Japan	Pre	2.00	2.92	-0.92	4.92	0.360
Japan	Post	3.93	3.24	0.69	7.17	
Switzerland	Pre	0.25	0.43	-0.18	0.68	**0.026**
Switzerland	Post	1.50	1.59	-0.09	3.09	

Source: Pharmaprojects (2021) and Trialtrove (2021). Antibiotic products were selected based on recorded therapeutic class. Distinctions were not made between novel classes of antibiotics and existing classes, but reformulations of existing antibiotics were excluded. Data were not split by phase to preserve the n number for the number of trials in Japan and Switzerland. Mean approvals per year and standard deviations were calculated for both the pre and post periods.

Interpretation of possible causes for changes in AMR-3-4

Due to the relatively low level of activity in the pharmaceutical industry in terms of the development of antibiotics or antimicrobials, it was not possible to assess any statistically significant differences. However, while the number of approved products was shown to not change over time in any analysis region or country (AMR-3), there is an observable trend that the number of trials for antimicrobials starting in each year increases in the post period, as does the number of products in trials in each year (AMR-4). However, in addition to the EU, this trend was observed in the other analysis regions, so the impact on the EU of the general pharmaceutical legislation is unknown.

1.9 ENVIRONMENTAL IMPACTS INDICATORS

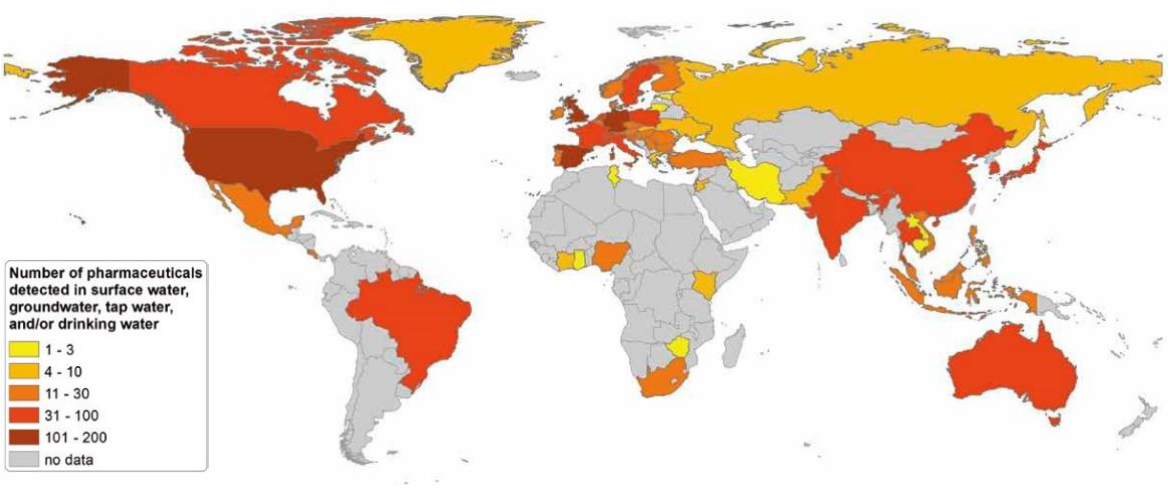
Indicator name	Indicator description
	Presence of pharmaceutical residues in the environment:
EI-1	Concentrations of pharmaceutical residues in the environment
	Emissions from manufacturing plants:
EI-2	Emission intensity/absolute emissions of GHG by the pharmaceutical industry

EI-1: Concentrations of pharmaceutical residues in the environment

Weber et al., (2014) documents that pharmaceutical residues have been detected in 71 countries worldwide in all five UN regional groups (Figure EI-1).[18] Pharmaceuticals were detected in surface water and sewage effluent, but also to a lesser extent on groundwater, manure, soil, and other environmental matrices.

Pharmaceuticals are often found in concentrations of 0.1 µg/L to 1.0 µg/L in rivers and lakes that receive wastewater. However, maximum concentrations in densely populated areas or downstream of sewage treatment plants may be considerably higher. Less data is available on pharmaceuticals in manure and soil, but residues have been detected in 28 countries, especially in the vicinity of intense animal husbandry.

Figure EI-1: Number of pharmaceuticals detected in surface water, groundwater, tap water, and/or drinking water



The report also concludes that the close to 600 active pharmaceutical substances that have been found in the environment belong to 6 therapeutic groups: antibiotics, analgesics, lipid-lowering drugs, beta-blockers, x-ray contrast media, and synthetic estrogens (Table EI-1.1).

[18]https://www.umweltbundesamt.de/sites/default/files/medien/378/publikationen/pharmaceuticals_in_the_environment_0.pdf

Table EI-1.1: Several globally marketed pharmaceuticals have been found in the aquatic environment of all UN regional groups.

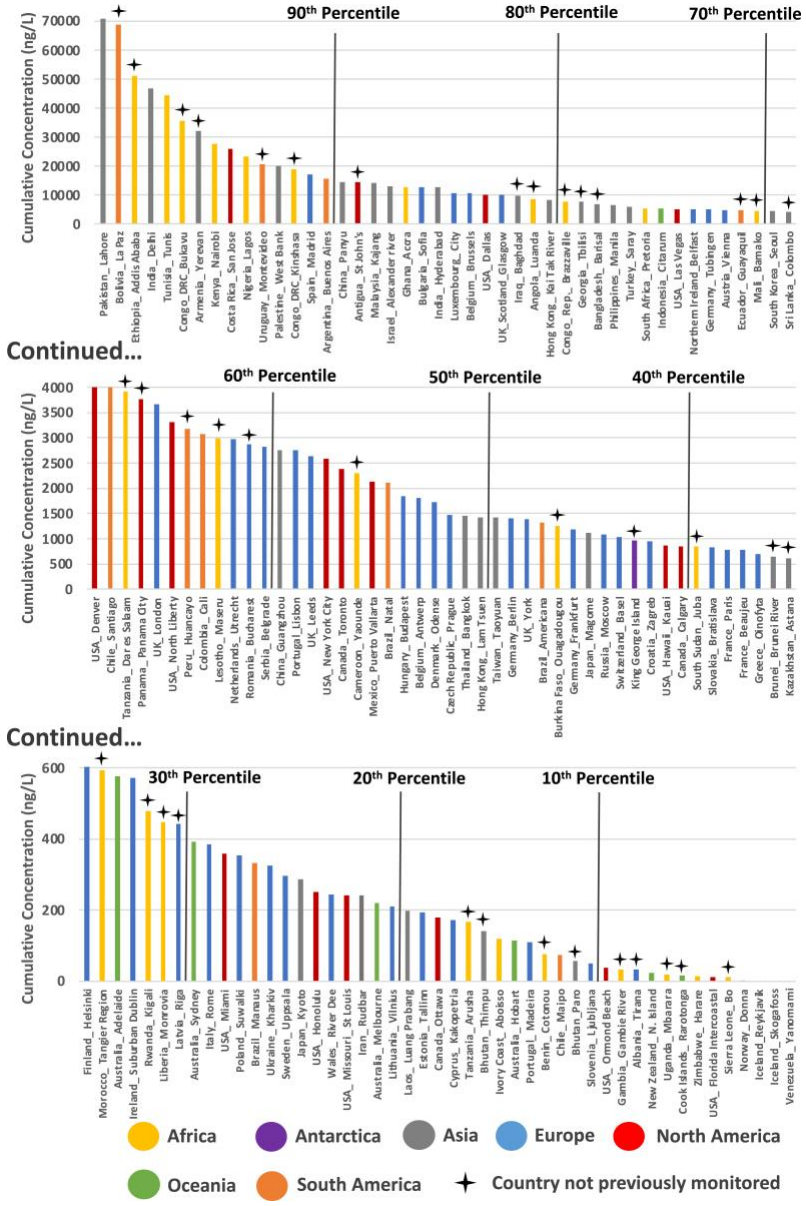
Pharmaceutical	Therapy Group	Number of countries worldwide in which pharmaceuticals have been found in the aquatic environment
Diclofenac	Analgesics	50
Carbamazepine	Antiepileptic drugs	48
Ibuprofen	Analgesics	47
Sulfamethoxazole	Antibiotics	47
Naproxen	Analgesics	45
Estrone	Estrogens	35
17-β-Estradiol	Estrogens	34
17-α-Ethinylestradiol	Estrogens	31
Trimethoprim	Antibiotics	29
Paracetamol	Analgesics	29
Clofibric acid	Lipid-lowering drugs	23
Ciprofloxacin	Antibiotics	20
Ofloxacin	Antibiotics	16
Estriol	Estrogens	15
Norfloxacin	Antibiotics	15
Acetylsalicylic acid	Analgesics	15

Source: Weber et al., (2014).

A more recent study by Wilkinson et al. (2022) covering 1,052 sampling sites located in 104 countries across all continents found that with the exception of Iceland and the Yanomami Village in Venezuela, at least one API was detected in all of the study sites.[19] Figure EI-1.2 shows that the highest mean cumulative concentration was observed in Lahore, Pakistan at 70.8 µg/L. The most polluted European samples were from a site in Madrid, Spain (mean 17.1 µg/L, maximum 59.5 µg/L).

[19] Wilkinson et al. Pharmaceutical pollution of the world's rivers. PNAS. 2022.

Figure EI-1.2: Cumulative API concentrations quantified across 137 studied river catchments organized by descending cumulative concentration (ng/L).

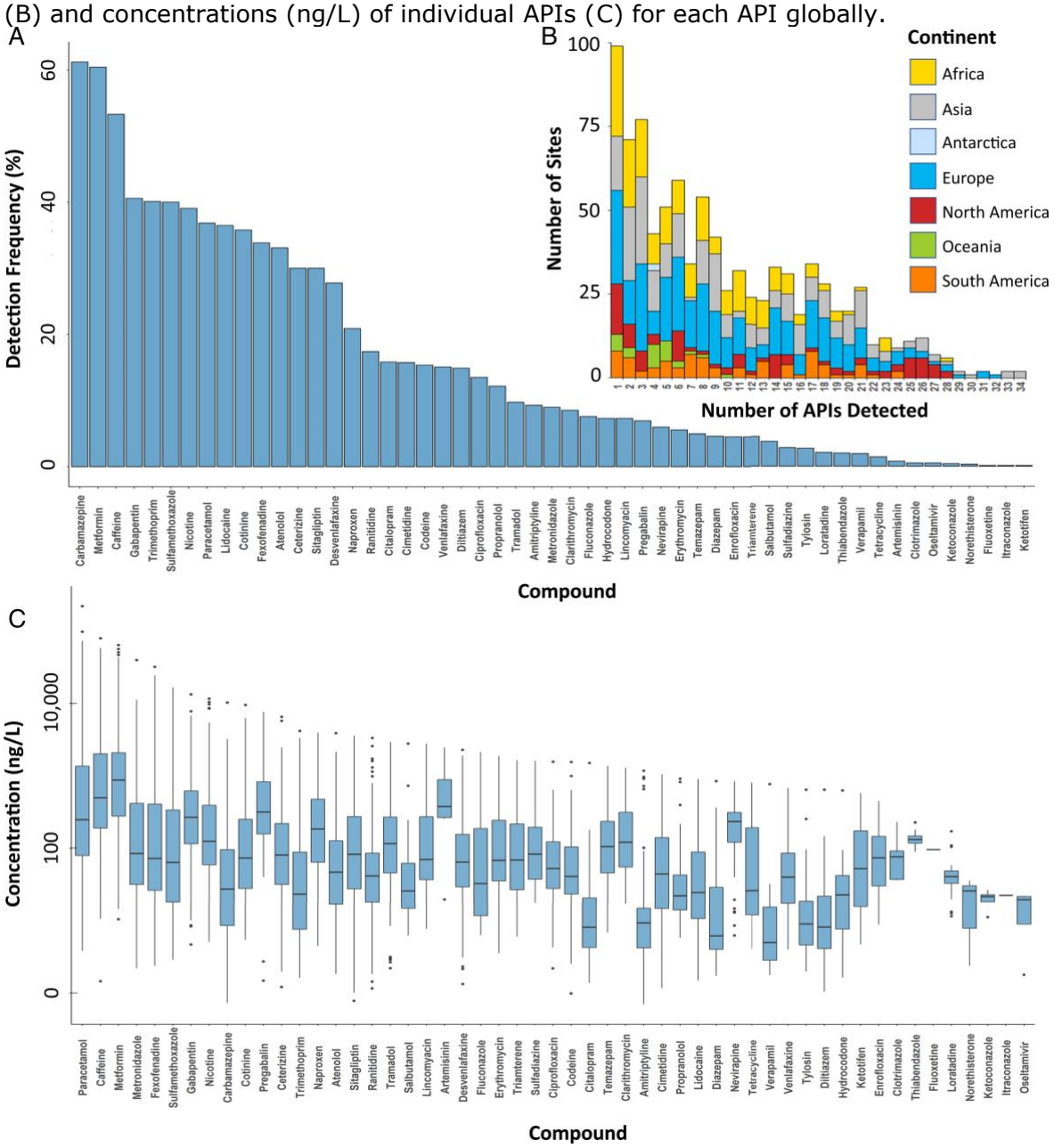


Source: Wilkinson et al. (2022)

Of the 61 targeted APIs in the study, 53 were detected in at least one sampling site. On a continental basis, 45 APIS were found in Europe, 39 in North America, 41 in Africa and 35 in South America (see Figure EI-1.3, panel B). Four APIs were detected across all continents, of which all are considered either lifestyle compounds or over-the-counter APIs: caffeine (stimulant and lifestyle compound), nicotine (stimulant and lifestyle compound), acetaminophen/paracetamol (analgesic), and cotinine (metabolite of a stimulant and lifestyle compound). An additional 14 APIs were detected in all continents except Antarctica: atenolol (β-blocker), carbamazepine (antiepileptic), cetirizine (antihistamine), citalopram (antidepressant), desvenlafaxine (antidepressant), fexofenadine (antihistamine), gabapentin (anticonvulsant), lidocaine (anesthetic), metformin (antihyperglycemic), naproxen (anti-inflammatory), sitagliptin (antihyperglycemic), temazepam (benzodiazepine for insomnia treatment), trimethoprim (antimicrobial), and venlafaxine (antidepressant).

Figure EI-1.3 (panel A) shows that for the detected APIs, overall detection frequencies ranged from 0.1% for fluoxetine (antidepressant), itraconazole (antifungal), and ketotifen (antihistamine), to 62% for carbamazepine within respective river catchments. Metformin and caffeine were also detected at over 50% of all the sampling sites worldwide.

Figure EI-1.3: Detection frequencies (A), number of APIs detected at sampling sites (B) and concentrations (ng/L) of individual APIs (C) for each API globally.



Source: Wilkinson et al. (2022)

EI-2: Emission intensity/absolute emissions of GHG by the pharmaceutical industry

Belkhir et al.,(2018) study the carbon footprint of the global pharmaceutical industry.[20] They examined the Pharma industry over a four-year period from 2012 to 2015 focusing on twenty five major Pharma companies that reported their scope 1 and scope 2 emissions in 2015 and concentrate 70% of the total sector revenues in 2015. Of those firms only fifteen reported their emissions consistently during 2012 -2015. The study found that the pharmaceutical sector is far from being a green sector. In fact, the sector's emission intensity in 2015 was 48.55 Mt-CO2e/$M, which is about 55% higher than that of the Automotive sector of 31.4 Mt-CO2e/$M for that same year. Similarly, in absolute value, the aggregate global emissions of the Pharma sector amount to about 52 MMt-CO2e in 2015 compared to about 46.4 MMt-CO2e emitted by the global automotive sector in that same year (where ”MMt” indicates Million of Metric tons).

[20] Lotfi Belkhir, Ahmed Elmeligi, Carbon footprint of the global pharmaceutical industry and relative impact of its major players, Journal of Cleaner Production, Volume 214, 2019, Pages 185-194, ISSN 0959-6526, https://doi.org/10.1016/j.jclepro.2018.11.204.

ANNEX A: QUANTITATIVE DATA SOURCES

Overview of the main databases available for Task 2 of the study

Database	Summary description
Trialtrove Informa Pharma proprietary clinical trial database	The Trialtrove database is a large database of clinical trial intelligence containing data on over 375,000 clinical trials in over 210 diseases in more than 150 countries. A global team of specialist analysts using information from over 30,000 clinical trial data sources curates the database as a continuously updated reference source for clinical trials research. Information from sources such as company websites, press releases, annual reports and investor presentations, papers in medical journals, and clinical trial registries, goes through a rigorous process of identification, checking, and cleaning before entry into the database by a dedicated analyst team of specialists. The data used in this report allows the tracking of the progress of drugs from Phase 1 to approval. While the dataset nominally ranges 1990-2021, the data thin out considerably in the early and most recent periods; therefore, most analyses focus on the 1998-2020 period. We transform the trial data such that an observation refers to the trial of a specific drug, for a specific indication (drugs may be tested for multiple indications), in a specific year. The resulting dataset tracks the progress of 28,167 drugs in 9 therapy areas of indications through 33,626 different trials. In total, 9,472 drugs were tested in the EU, 15,774 in the USA, and 3,170 in Japan (the sum across regions exceeds the total number of drugs tested, as some drugs were tested in multiple regions for different indications). We track drug development through up to 3 phases of clinical trials. We count a trial as completed successfully if we see the same drug (in the same indication) being trialled in a higher phase at a later point in time. Thus, if we see a drug in a Phase 1 trial in 2002 and in a Phase 2 trial in 2003, we conclude that the Phase 1 trial in 2002 was completed successfully. We count the third and final phase as completed successfully if we see a drug being approved for sale. The

	final dataset contains a total of 13,849 Phase 1 trials, 16,484 Phase 2 trials, and 8,168 Phase 3 trials. Caveats: We observe the geographic location of a trial in the Trialtrove data, which sometimes indicates that a trial took place in multiple locations (e.g., in the EU and the USA jointly). To circumvent this, we added data on a drug's originator (i.e., the original developer) and the respective location from Informa Pharma's Pharmaprojects database. However, for some trials, it remains unclear which jurisdiction a trial should be counted under. We drop some trials that were either i) conducted in multiple geographies, or ii) for which the location of the originator could not be reliably asserted. Combinatorial drug treatments (i.e., trials testing a combination of multiple, different drugs) have been added to the dataset. However, we do not reliably observe when or if combinatorial treatments are approved for marketing. Therefore, we include combinatorial treatments in the analysis of indicators RI-1, RI-2, and RI-3, but we exclude them for RI-4 and RI-6. Data on approval merged from the Pharmaprojects database are only available for around 5,000 drugs, about 2,200 of which could be matched to the analysis dataset. Therefore, the phase progressions in Phase 1 and Phase 2 are not directly comparable to those in Phase 3 and the overall likelihood of approval. However, the overall rate of drugs that end up being approved for marketing is around 10%, which corresponds to experience. The level of data availability in the Trialtrove database is not constant over time. For example, in the figure showing Phase 1 candidate drugs, we see a strong increase in trials over time and close to zero trials in the early 1990s. This is due to the construction of the database and data collection procedures, and is not indicative of a corresponding rise in clinical trials. In the statistical analysis, this is accounted for through the inclusion of year fixed-effects.
Sitetrove Informa Pharma proprietary clinical trial site and investigator database	The Sitetrove database is a large database of clinical trial intelligence containing data on over 510,000 investigators from more than 185,000 clinical trial sites in over 180 countries.

	The database is useful in identifying clinical trial and investigator involvement in the development of drugs, thus complementing Trialtrove in supported detailed county level analysis of clinical trials. The database offers features such as investigator tiering and patient count data, complemented by dynamic and exportable visualizations to aid in data sharing and use.
Pharmaprojects Informa Pharma pharmaceutical product database	The Pharmaprojects database is a large database of pipeline and marketed drug intelligence containing data on over 90,000 drugs in more than 150 countries. A global team of specialist analysts using information on drugs curates the database as a continuously updated reference source for pipeline and marketed drugs. Information from sources such as company websites, press releases, annual reports and investor presentations, papers in medical journals, and clinical trial registries, goes through a rigorous process of identification, checking, and cleaning before entry into the database by a dedicated analyst team of specialists. All drug approval data described in this report are based on the data contained in Pharmaprojects and Biomedtracker as of August 2021. The base dataset for IEC-1-4 contained 4,981 products with a known approval date anywhere in the world. The approval year was set based on first approval only; the number and dates of subsequent approvals relating to indication expansion were not counted. The origin of the medical product was set by the HQ country of the originator company as recorded in Pharmaprojects.
Biomedtracker Informa Pharma proprietary pharmaceutical product database	Informa Pharma's Biomedtracker pipeline database provides real time analysis of major market moving events in the pharma and biotech industry, tracking and analysing events in drug development in real time with a US focus. Biomedtracker analysts monitor companies, trials, deals, and regulatory meetings to capture and interpret the most critical events. The database offers features such as likelihood of approval for individual drugs, detailed clinical, regulatory, and partnership event analysis, revenue models, FDA advisory committee insights, analysis of voting patterns of FDA advisory committee

	members, commentary on past meetings, and data on life science company deals including licensing deals and mergers and acquisitions
Datamonitor Healthcare Informa Pharma proprietary pharmaceutical industry database	Detailed company and market specific research and analysis enable expert insight and rapid understanding of complex market dynamics, including forecasts presented as interactive market models. The PharmaVitae module within Datamonitor Healthcare contains detailed company reported data on metrics such as revenues, profits, and R&D spending. Datamonitor Healthcare includes timely, in depth research and expert analysis, with coverage of more than 65 indications. Accurate and objective marketed and pipeline drug sales forecasts and segmented patient-based disease forecasts feature event sensitive analysis and advanced display options. Pipelines are analysed by indication and company, and insights are provided on corporate strategies and trends. Analysis of pricing and reimbursement by indication, plus market access trends and themes are complemented by epidemiology data across all major therapy areas based on expert reviews of the available epidemiological literature to identify the most reliable data sources
Utrecht University MAA database	The Utrecht MAA database provides data on all medicinal products that obtained a centralised marketing authorisation in Europe since the establishment of the European Medicines Agency (EMA) on January 1st 1995 to December 31st 2020. The dataset consists of 1,456 authorised products, of which 317 were approved under Regulation 2309/93 and 1,139 under Regulation 726/2004. For post-marketing data an end-of-follow-up date of December 31st 2020 was used.
EU shortages database dependent on permission from the European Commission	Technopolis has developed a database of reported shortages for the European Commission using shortage datasets received from National Competent Authorities and linked those to IQVIA MIDAS database. It includes over 100,000 reported shortages with 22,500 medicines in shortages identified from 20 European countries over the years of 2007-2021.
IQVIA MIDAS database	Our consortium has intimate familiarity of using the IQVIA dataset through a number of previous studies. The IQVIA

	dataset was made available by the European Commission through a TPA and provided sales volume and revenue data on medicines 2008-2020, for the geographical area Europe and comparator markets.

ANNEX B: LIST OF PRODUCTS IN THE EFPIA-ECIPE REPORT (2020)

Broader Pharmaceutical Category	Pharmaceutical Category	CN Code	Product name
Active Pharmaceutical Ingredients (APIs)	Active Pharmaceutical Ingredients (APIs)	291462	Coenzyme Q10 "ubidecarenone (INN)"
		291469	Quinones (excl. anthraquinone and coenzyme Q10 "ubidecarenone (INN)")
		291639	Aromatic monocarboxylic acids, their anhydrides, halides, peroxides, peroxyacids and their halogenated, sulphonated, nitrated or nitrosated derivatives (excl. benzoic acid, its salts and esters, benzoyl peroxide, benzoyl chloride, phenylacetic acid and its salts, and inorganic or organic compounds of mercury whether or not chemically defined)
		291821	Salicylic acid and its salts (excl. inorganic or organic compounds of mercury)
		291822	o-Acetylsalicylic acid, its salts and esters
		291823	Esters of salicylic acid and their salts (excl. o-acetylsalicylic acid, its salts and esters)
		291899	Carboxylic acids with additional oxygen function and their anhydrides, halides, peroxides and peroxyacids; their halogenated, sulphonated, nitrated or nitrosated derivatives (excl. only with alcohol, phenol, aldehyde or ketone function, and 2,4,5-T (ISO) [2,4,5-trichlorophenoxyacetic acid] and its salts and esters)
		292146	Amfetamine (INN), benzfetamine (INN), dexamfetamine (INN), etilamfetamine (INN), fencamfamine (INN), lefetamine (INN), levamfetamine (INN), mefenorex (INN) and phentermine (INN), and salts thereof
		292149	Aromatic monoamines and derivatives; salts thereof (excl. aniline, toluidines, diphenylamine, 1-naphthylamine "alpha-naphthylamine", 2-naphthylamine "beta-naphthylamine" and their derivatives, and salts thereof, and amfetamine (INN), benzfetamine (INN), dexamfetamine (INN), etilamfetamine (INN), fencamfamine (INN), lefetamine (INN), levamfetamine (INN), mefenorex (INN) and phentermine (INN), and salts thereof)
		292214	Dextropropoxyphene (INN) and its salts
		292219	Amino-alcohols, their ethers and esters; salts thereof (other than those containing > one kind of oxygen function and excl. monoethanolamine, diethanolamine, dextropropoxyphene (INN), their salts, triethanolamine, diethanolammonium perfluorooctane sulphonate, methyldiethanolamine, ethyldiethanolamine and 2-(N,N-Diisopropylamino)ethanol)
		292229	Amino-naphthols and other amino-phenols, their ethers and esters; salts thereof (excl. those containing > one kind of oxygen function; aminohydroxynaphthalenesulphonic acids and their salts)
		292231	Amfepramone (INN), methadone (INN) and normethadone (INN), and salts thereof
		292241	Lysine and its esters; salts thereof
		292244	Tilidine (INN) and its salts
		292249	Amino-acids and their esters; salts thereof (excl. those with > one kind of oxygen function, lysine and its esters, and salts thereof, and glutamic acid, anthranilic acid, tilidine (INN), and salts thereof)
		292250	Amino-alcohol-phenols, amino-acid-phenols and other amino-compounds with oxygen function (excl. amino-alcohols, amino-naphthols and other amino-phenols, their ethers and esters and salts

			thereof, amino-aldehydes, amino-ketones and amino-quinones, and salts thereof, amino-acids and their esters and salts thereof)
		292320	Lecithins and other phosphoaminolipids, whether or not chemically defined
		292411	Meprobamate (INN)
		292424	Ethinamate (INN)
		292429	Cyclic amides, incl. cyclic carbamates, and their derivatives; salts thereof (excl. ureines and their derivatives, salts thereof, 2-acetamidobenzoic acid "N-acetylanthranilic acid" and its salts, ethinamate (INN) and alachlor (ISO))
		292512	Glutethimide (INN)
		292529	Imines and their derivatives; salts thereof (excl. chlordimeform (ISO))
		292630	Fenproporex (INN) and its salts; methadone (INN)-intermediate "4-cyano-2-dimethylamino-4,4-diphenylbutane"
		293190	Separate chemically defined organo-inorganic compounds (excl. organo-sulphur, mercury, tetramethyl lead, tetraethyl lead and tributyltin compounds, and organo-phosphorous derivatives)
		293220	Lactones
		293311	Phenazone "antipyrin" and its derivatives
		293319	Heterocyclic compounds with nitrogen hetero-atom[s] only, containing an unfused pyrazole ring, whether or not hydrogenated, in the structure (excl. phenazone "antipyrin" and its derivatives)
		293321	Hydantoin and its derivatives
		293329	Heterocyclic compounds with nitrogen hetero-atom[s] only, containing an unfused imidazole ring, whether or not hydrogenated, in the structure (excl. hydantoin and its derivatives, and products of subheading 3002 10)
		293331	Pyridine and its salts
		293332	Piperidine and its salts
		293333	Alfentanil (INN), anileridine (INN), bezitramide (INN), bromazepam (INN), difenoxin (INN), diphenoxylate (INN), dipipanone (INN), fentanyl (INN), ketobemidone (INN), methylphenidate (INN), pentazocine (INN), pethidine (INN), pethidine (INN) intermediate A, phencyclidine (INN) "PCP", phenoperidine (INN), pipradol (INN), piritramide (INN), propiram (INN) and trimeperidine (INN), and salts thereof
		293339	Heterocyclic compounds with nitrogen hetero-atom[s] only, containing an unfused pyridine ring, whether or not hydrogenated, in the structure (excl. pyridine, piperidine, alfentanil (INN), anileridine (INN), bezitramide (INN), bromazepam (INN), difenoxin (INN), diphenoxylate (INN), dipipanone (INN), fentanyl (INN), ketobemidone (INN), methylphenidate (INN), pentazocine (INN), pethidine (INN), pethidine (INN) intermediate A, phencyclidine (INN) "PCP", phenoperidine (INN), pipradol (INN), piritramide (INN), propiram (INN), trimeperidine (INN), and salts thereof, and inorganic or organic compounds of mercury)
		293341	Levorphanol (INN) and its salts
		293349	Heterocyclic compounds with nitrogen hetero-atom[s] only, containing in the structure a quinoline or isoquinoline ring-system, whether or not hydrogenated, but not further fused (excl. levorphanol (INN) and its salts, and inorganic or organic compounds of mercury)

		293352	Malonylurea "barbituric acid" and its salts
		293353	Allobarbital (INN), amobarbital (INN), barbital (INN), butalbital (INN), butobarbital (INN), cyclobarbital (INN), methylphenobarbital (INN), pentobarbital (INN), phenobarbital (INN), secbutabarbital (INN), secobarbital (INN) and vinylbital (INN), and salts thereof
		293354	Derivatives of malonylurea "barbituric acid" and salts thereof (excl. salts of malonylurea)
		293355	Loprazolam (INN), mecloqualone (INN), methaqualone (INN) and zipeprol (INN), and salts thereof
		293359	Heterocyclic compounds with nitrogen hetero-atom[s] only, containing a pyrimidine ring, whether or not hydrogenated, or piperazine ring in the structure (excl. malonylurea "barbituric acid" and its derivatives, allobarbital (INN), amobarbital (INN), barbital (INN), butalbital (INN), butobarbital (INN), cyclobarbital (INN), methylphenobarbital (INN), pentobarbital (INN), phenobarbital (INN), secbutabarbital (INN), secobarbital (INN), vinylbital (INN), loprazolam (INN), mecloqualone (INN), methaqualone (INN) and zipeprol (INN), and salts thereof)
		293369	Heterocyclic compounds with nitrogen hetero-atom[s] only, containing an unfused triazine ring, whether or not hydrogenated, in the structure (excl. melamine)
		293371	6-Hexanelactam "epsilon-caprolactam"
		293372	Clobazam (INN) and methyprylon (INN)
		293379	Lactams (excl. 6-hexanelactam "epsilon-caprolactam", clobazam (INN), methyprylon (INN), and inorganic or organic compounds of mercury)
		293391	Alprazolam (INN), camazepam (INN), chlordiazepoxide (INN), clonazepam (INN), clorazepate, delorazepam (INN), diazepam (INN), estazolam (INN), ethyl loflazepate (INN), fludiazepam (INN), flunitrazepam (INN), flurazepam (INN), halazepam (INN), lorazepam (INN), lormetazepam (INN), mazindol (INN), medazepam (INN), midazolam (INN), nimetazepam (INN), nitrazepam (INN), nordazepam (INN), oxazepam (INN), pinazepam (INN), prazepam (INN), pyrovalerone (INN), temazepam (INN), tetrazepam (INN) and triazolam (INN), and salts thereof
		293399	Heterocyclic compounds with nitrogen hetero-atom[s] only (excl. those containing an unfused pyrazole, imidazole, pyridine or triazine ring, whether or not hydrogenated, a quinoline or isoquinoline ring-system, not further fused, whether or not hydrogenated, a pyrimidine ring, whether or not hydrogenated, or piperazine ring in the structure, and lactams, alprazolam (INN), camazepam (INN), chlordiazepoxide (INN), clonazepam (INN), clorazepate, delorazepam (INN), diazepam (INN), estazolam (INN), ethyl loflazepate (INN), fludiazepam (INN), flunitrazepam (INN), flurazepam (INN), halazepam (INN), lorazepam (INN), lormetazepam (INN), mazindol (INN), medazepam (INN), midazolam (INN), nimetazepam (INN), nitrazepam (INN), nordazepam (INN), oxazepam (INN), pinazepam (INN), prazepam (INN), pyrovalerone (INN), temazepam (INN), tetrazepam (INN) and triazolam (INN), salts thereof and azinphos-methyl (ISO))
		293410	Heterocyclic compounds containing an unfused thiazole ring, whether or not hydrogenated, in the structure
		293420	Heterocyclic compounds containing in the structure a benzothiazole ring-system, whether or not hydrogenated, but not further fused (excl. inorganic or organic compounds of mercury)
		293430	Heterocyclic compounds containing in the structure a phenothiazine ring-system, whether or not hydrogenated, but not further fused

		293491	Aminorex (INN), brotizolam (INN), clotiazepam (INN), cloxazolam (INN), dextromoramide (INN), haloxazolam (INN), ketazolam (INN), mesocarb (INN), oxazolam (INN), pemoline (INN), phendimetrazine (INN), phenmetrazine (INN) and sufentanil (INN), and salts thereof
		293499	Nucleic acids and their salts, whether or not chemically defined; heterocyclic compounds (excl. with oxygen only or with nitrogen hetero-atom[s] only, compounds containing in the structure an unfused thiazole ring or a benzothiazole or phenothiazine ring-system, not further fused and aminorex (INN), brotizolam (INN), clotiazepam (INN), cloxazolam (INN), dextromoramide (INN), haloxazolam (INN), ketazolam (INN), mesocarb (INN), oxazolam (INN), pemoline (INN), phendimetrazine (INN), phenmetrazine (INN), sufentanil (INN), and salts thereof, and inorganic or organic compounds of mercury whether or not chemically defined, and products of 3002 10)
		293590	Sulphonamides (excl. perfluorooctane sulphonamides)
		293621	Vitamins A and their derivatives, used primarily as vitamins
		293622	Vitamin B1 and its derivatives, used primarily as vitamins
		293623	Vitamin B2 and its derivatives, used primarily as vitamins
		293624	D-Pantothenic or DL-pantothenic acid "Vitamin B3 or B5" and their derivatives, used primarily as vitamins
		293625	Vitamin B6 and its derivatives, used primarily as vitamins
		293626	Vitamin B12 and its derivatives, used primarily as vitamins
		293627	Vitamin C and its derivatives, used primarily as vitamins
		293628	Vitamin E and its derivatives, used primarily as vitamins
		293629	Vitamins and their derivatives, used primarily as vitamins, unmixed (excl. vitamins A, B1, B2, B3, B5, B6, B12, C, E and their derivatives)
		293690	Provitamins and mixtures of vitamins, of provitamins or of concentrates, whether or not in any solvent, and natural concentrates
		293711	Somatropin, its derivatives and structural analogues, used primarily as hormones
		293712	Insulin and its salts, used primarily as hormones
		293719	Polypeptide hormones, protein hormones and glycoprotein hormones, their derivatives and structural analogues, used primarily as hormones (excl. somatropin, its derivatives and structural analogues, and insulin and its salts)
		293721	Cortisone, hydrocortisone, prednisone "dehydrocortisone" and prednisolone "dehydrohydrocortisone"
		293722	Halogenated derivatives of corticosteroidal hormones
		293723	Oestrogens and progestogens
		293729	Steroidal hormones, their derivatives and structural analogues, used primarily as hormones (excl. cortisone, hydrocortisone, prednisone "dehydrocortisone", prednisolone "dehydrohydrocortisone", halogenated derivatives of corticosteroidal hormones, oestrogens and progestogens)
		293750	Prostaglandins, thromboxanes and leukotrienes, their derivatives and structural analogues, used primarily as hormones
		293790	Hormones, natural or reproduced by synthesis; derivatives and structural analogues thereof, used primarily as hormones (excl. polypeptide hormones, protein hormones, glycoprotein hormones, steroidal hormones, catecholamine hormones, prostaglandins,

			thromboxanes and leukotrienes, their derivatives and structural analogues, and amino-acid derivatives, and products of 3002 10)
		293810	Rutoside "rutin" and its derivatives
		293890	Glycosides, natural or reproduced by synthesis, and their salts, ethers, esters and other derivatives (excl. rutoside "rutin" and its derivatives)
		293911	Concentrates of poppy straw; buprenorphine (INN), codeine, dihydrocodeine (INN), ethylmorphine, etorphine (INN), heroin, hydrocodone (INN), hydromorphone (INN), morphine, nicomorphine (INN), oxycodone (INN), oxymorphone (INN), pholcodine (INN), thebacon (INN) and thebaine, and salts thereof
		293919	Alkaloids of opium and their derivatives, and salts thereof (excl. concentrates of poppy straw; buprenorphine (INN), codeine, dihydrocodeine (INN), ethylmorphine, etorphine (INN), heroin, hydrocodone (INN), hydromorphone (INN), morphine, nicomorphine (INN), oxycodone (INN), oxymorphone (INN), pholcodine (INN), thebacon (INN) and thebaine, and salts thereof)
		293920	Alkaloids of cinchona and their derivatives; salts thereof
		293930	Caffeine and its salts
		293941	Ephedrine and its salts
		293942	Pseudoephedrine (INN) and its salts
		293943	Cathine (INN) and its salts
		293944	Norephedrine and its salts
		293949	Ephedrines and their salts (excl. ephedrine, pseudoephedrine (INN), cathine (INN), norephedrine, and their salts)
		293951	Fenetylline (INN) and its salts
		293959	Theophylline and aminophylline "theophylline-ethylenediamine" and their derivatives, and salts thereof (excl. fenetylline (INN) and its salts)
		293961	Ergometrine (INN) and its salts
		293962	Ergotamine (INN) and its salts
		293963	Lysergic acid and its salts
		293969	Alkaloids of rye ergot and their derivatives; salts thereof (excl. lysergic acid, ergotamine and ergometrine, and their salts)
		293971	Cocaine, ecgonine, levometamfetamine, metamfetamine (INN), metamfetamine racemate, and salts, esters and other derivatives thereof
		293979	Vegetal alkaloids, natural or reproduced by synthesis, and their salts, ethers, esters and other derivatives (excl. alkaloids of opium, alkaloids of cinchons, theophylline, aminophylline "theophylline-ethylenediamine" alkaloids of rye ergot and their salts and derivatives, cocaine, ecgonine, levometamfetamine, metamfetamine (INN), metamfetamine racemate, and salts, esters and other derivatives thereof, caffeine and ephedrines, and their salts)
		293980	Non-vegetal alkaloids, natural or reproduced by synthesis, and their salts, ethers, esters and other derivatives
		294200	Separate chemically defined organic compounds, n.e.s.

		300190	Dried glands and other organs for organo-therapeutic uses, whether or not powdered; heparin and its salts; other human or animal substances prepared for therapeutic or prophylactic uses, n.e.s.
		300213	Immunological products, unmixed, not put up in measured doses or in forms or packings for retail sale
	Antibiotics APIs	294110	Penicillins and their derivatives with a penicillanic acid structure; salts thereof
		294120	Streptomycins and their derivatives; salts thereof
		294130	Tetracyclines and their derivatives; salts thereof
		294140	Chloramphenicol and its derivatives; salts thereof
		294150	Erythromycin and its derivatives; salts thereof
		294190	Antibiotics (excl. penicillins and their derivatives with a penicillanic acid structure, salts thereof, streptomycins, tetracyclines, chloramphenicol and erythromycin, their derivatives and salts thereof)
Semi Finished Products (SFPs)	Semi Finished Products (SFPs)	300214	Immunological products, mixed, not put up in measured doses or in forms or packings for retail sale
		300310	Medicaments containing penicillins or derivatives thereof with a penicillanic acid structure, or streptomycins or derivatives thereof, not in measured doses or put up for retail sale
		300320	Medicaments containing antibiotics, not in measured doses or put up for retail sale (excl. medicaments containing penicillins or derivatives thereof with a penicillanic acid structure, or streptomycins or derivatives thereof)
		300331	Medicaments containing insulin, not in measured doses or put up for retail sale
		300339	Medicaments containing hormones or steroids used as hormones, not containing antibiotics, not in measured doses or put up for retail sale (excl. those containing insulin)
		300341	Medicaments containing ephedrine or its salts, not containing hormones, steroids used as hormones or antibiotics, not in measured doses or put up for retail sale
		300342	Medicaments containing pseudoephedrine (INN) or its salts, not containing hormones, steroids used as hormones or antibiotics, not in measured doses or put up for retail sale
		300343	Medicaments containing norephedrine or its salts, not containing hormones, steroids used as hormones or antibiotics, not in measured doses or put up for retail sale
		300349	Medicaments containing alkaloids or derivatives thereof, not containing hormones, steroids used as hormones or antibiotics, not in measured doses or put up for retail sale (excl. containing ephedrine, pseudoephedrine (INN), norephedrine or their salts)
		300360	Medicaments containing any of the following antimalarial active principles: artemisinin (INN) for oral ingestion combined with other pharmaceutical active ingredients, or amodiaquine (INN); artelinic acid or its salts; artenimol (INN); artemotil (INN); artemether (INN); artesunate (INN); chloroquine (INN); dihydroartemisinin (INN); lumefantrine (INN); mefloquine (INN); piperaquine (INN); pyrimethamine (INN) or sulfadoxine (INN), not containing hormones, steroids used as hormones or antibiotics, not in measured doses or put up for retail sale
		300390	Medicaments consisting of two or more constituents mixed together for therapeutic or prophylactic uses, not in measured doses or put up for retail sale (excl. antibiotics containing hormones or steroids used as hormones, but not containing antibiotics, alkaloids or derivatives thereof, hormones, antibiotics, antimalarial active principles or goods of heading 3002, 3005 or 3006)

Human Medicinal Products (HMPs)	Finished Pharmaceutical Products (FPPs)	300215	Immunological products, put up in measured doses or in forms or packings for retail sale
		300431	Medicaments containing insulin but not antibiotics, put up in measured doses "incl. those for transdermal administration" or in forms or packings for retail sale
		300432	Medicaments containing corticosteroid hormones, their derivatives or structural analogues but not antibiotics, put up in measured doses "incl. those for transdermal administration" or in forms or packings for retail sale
		300439	Medicaments containing hormones or steroids used as hormones but not antibiotics, put up in measured doses "incl. those for transdermal administration" or in forms or packings for retail sale (excl. medicaments containing insulin or corticosteroid hormones, their derivatives or structural analogues)
		300441	Medicaments containing ephedrine or its salts, not containing hormones, steroids used as hormones or antibiotics, put up in measured doses "incl. those for transdermal administration" or in forms or packings for retail sale
		300442	Medicaments containing pseudoephedrine (INN) or its salts, not containing hormones, steroids used as hormones or antibiotics, put up in measured doses "incl. those for transdermal administration" or in forms or packings for retail sale
		300443	Medicaments containing norephedrine or its salts, not containing hormones, steroids used as hormones or antibiotics, put up in measured doses "incl. those for transdermal administration" or in forms or packings for retail sale
		300449	Medicaments containing alkaloids or derivatives thereof, not containing hormones, steroids used as hormones or antibiotics, put up in measured doses "incl. those for transdermal administration" or in forms or packings for retail sale (excl. containing ephedrine, pseudoephedrine (INN), norephedrine or their salts)
		300450	Medicaments containing provitamins, vitamins, incl. natural concentrates and derivatives thereof used primarily as vitamins, put up in measured doses "incl. those for transdermal administration" or in forms or packings for retail sale (excl. containing antibiotics, hormones, alkaloids, or their derivatives)
		300460	Medicaments containing any of the following antimalarial active principles: artemisinin (INN) for oral ingestion combined with other pharmaceutical active ingredients, or amodiaquine (INN); artelinic acid or its salts; artenimol (INN); artemotil (INN); artemether (INN); artesunate (INN); chloroquine (INN); dihydroartemisinin (INN); lumefantrine (INN); mefloquine (INN); piperaquine (INN); pyrimethamine (INN) or sulfadoxine (INN), put up in measured doses "incl. those for transdermal administration" or in forms or packings for retail sale (excl. containing antibiotics, hormones, alkaloids, provitamins, vitamins, or their derivatives)
		300490	Medicaments consisting of mixed or unmixed products for therapeutic or prophylactic purposes, put up in measured doses "incl. those for transdermal administration" or in forms or packings for retail sale (excl. containing antibiotics, hormones or steroids used as hormones, alkaloids, provitamins, vitamins, their derivatives or antimalarial active principles)
	Antibiotics Finished Pharmaceutical Products (FPPs)	300410	Medicaments containing penicillins or derivatives thereof with a penicillanic acid structure, or streptomycins or derivatives thereof, put up in measured doses "incl. those for transdermal administration" or in forms or packings for retail sale
		300420	Medicaments containing antibiotics, put up in measured doses "incl. those for transdermal administration" or in forms or packings for retail sale (excl. medicaments containing penicillins or derivatives thereof with a penicillanic structure, or streptomycines or derivatives thereof)

	Vaccines	300220	Vaccines for human medicine

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