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ANNEX 1: PROCEDURAL INFORMATION

– *Lead DG, Decide reference and Work Programme reference.*

The Directorate General for Health and Food Safety (DG SANTE) is the lead DG on the initiative for the Pharmaceutical Strategy for Europe.

The initiative is in the European Commission's Work Programme for 2022, COM(2021)645 final, under the heading "Promoting our European Way of Life". The initiative has received the validation in the Agenda Planning on 25 March 2021 (reference PLAN/2021/10601) and the Inception Impact Assessment was published on 7 April 2021.

– *Organisation and timing.*

An inter-service steering group (ISSG) for the implementation of the Pharmaceutical Strategy for Europe was established. The ISSG specifically discussed matters relating to the evaluation and impact assessment of the general pharmaceutical legislation to ensure that they met the necessary standards for quality, impartiality and usefulness and written consultations on draft key documents took place; the comments of the ISSG were carefully considered in the development of the evaluation and impact assessment.

Along with the Secretariat-General and Legal Service, the following Commission services took part in the ISSG: DG Health and Food Safety (SANTE) DG Employment (EMPL); DG Communications Networks, Content and Technology (CONNECT); DG Internal Market, Industry, Entrepreneurship and SMEs (GROW); DG for Research and Innovation (RTD); Joint Research Centre (JRC); DG Trade (TRADE), DG International Partnerships (INTPA); DG Eurostat – European statistics (ESTAT); DG Environment (ENV); DG Energy (ENER); DG Economical and Financial Affairs (ECFIN); DG Competition (COMP), DG Climate Action (CLIMA) and DG European Health Emergency Preparedness and Response Authority (HERA).

– *Consultation of the Regulatory Scrutiny Board.*

The file benefitted from an upstream meeting with the Regulatory Scrutiny Board (RSB) on 26 January 2022. A first version of this Impact Assessment Report – with the Evaluation Report annexed – was submitted to the RSB on 22 June 2022, the meeting took place on 19 July and the RSB written report was received on 22 July 2022. The Board's overall opinion was negative and it issued the following findings:

(1) The report is not sufficiently precise about the key factors that cause unequal access to medicines and their affordability, and what exactly determines the observed differences between Member States. It is not clear if the revision will have a direct impact on access and affordability of medicines or it provides only an enabling framework to reach these objectives.
(2) The report does not clearly demonstrate the effectiveness of new incentive measures. It is not clear how the market launch conditionality and the transferable exclusivity voucher for AMR products will work. Possible counter-effects affecting the access-affordability trade-off are not sufficiently assessed.

(3) The report is not sufficiently clear on the impacts of options on innovation and competitiveness for the EU pharmaceutical ecosystem, including SMEs, and how this will affect access to and affordability of medicines for patients.
(4) The report does not sufficiently demonstrate the EU-added value, nor the proportionality of the preferred option.

The table below lists the changes in response to the recommendations of the RSB in its opinion. In addition, targeted corrections and amendments have been included in the new version of the impact assessment report to address the technical comments provided by the RSB to DG SANTE.

Recommendations of the RSB	**Modifications in the impact assessment report in response to these recommendations**
(1) The report should analyse and present, in greater detail, the multiplicity of factors (and relative determinants) that lead to accessible, affordable and quality medicinal products while separating more clearly the issues caused by business decisions from those resulting from divergent public policy decisions of Member States' authorities. It should discuss the influence of decisions taken at Member State level and how these decisions emerge from different public policy approaches and procedures in Member States (e.g. assessment of the relative effectiveness of new medicines, their therapeutic added value or different political spending policies, timing of new launches, etc). The report should clearly present and substantiate with evidence the mix of problem drivers that are causing underperformance on the ground and clearly indicate where this revision can realistically improve the situation, also taking into account related initiatives.	In sections 2.1 and 2.2, expanded respectively problem definition, drivers on access and affordability and added a new Annex 14 to describe further factors for access and business decision and different pricing policies in Member States. Furthermore, throughout the report clarified the general pharmaceutical legislation as enabling framework for these two objectives, including in section 2, and elaborated on related initiatives such as the SPC revision, e.g. in sections 7.1 and 7.3. In the analysis of the options (section 6), especially dealing with measures to improve market access, those factors are taken into account.
(2) The report should describe the available information about the current negotiation dynamics between Member States and industry, e.g. to what extent industry already reflects different purchasing power levels in their pricing decisions. On that basis, it should analyse how the new incentives and obligations for placing a medicines on the market in all Member States within two years will change these dynamics in terms of negotiating power and tactics and what the projected impact would be on Member States' health care systems. The stakeholder views from both industry and Member States should be clearly presented throughout the	The new Annex 14 describes industry's sequencing of market launch in view of referencing pricing as an example of the role of different purchasing power levels of the Member States. In sections 6.1.1.3 and 6.1.4, increased negotiation power of Member States from the market launch measure and impact on compliance and practical details is taken into account. Views of industry and Member States elaborated

report. The report should outline possible trade-offs (in terms of manufacturers' incentives) between expanding access to and improve affordability of new medicines.	in e.g. sections 6.1.1.3 and 6.2. In section 6.1.4, clarified that for health systems, the market launch measure is a win-win in terms of access and affordability, rather than a trade-off.
(3) The impact of legal uncertainty for companies as regards materialising the additional regulatory protection period should be discussed in depth and should be substantiated with evidence given that the conditional extra years are dependent on factors outside of their control, in particular Member States' behaviour. The report should assess the impacts of this legal uncertainty, including on the launch of new innovation and future pricing decisions. It should assess whether shortening the standard regulatory protection period from eight to six years is likely to lead to higher average prices for health systems during the protection period, including by learning from third countries' experience of such shorter regulatory protection. The report should discuss more thoroughly how legal certainty for innovative businesses can be adequately ensured. It should describe how the Transparency Directive affects and influences Member States' and companies' behaviour and explain how possible non-cooperative behaviour from Member States' authorities can be avoided. Additionally, the report should ensure consistency and clarity when describing the different regulatory protection options when using concepts as standard and baseline protection periods.	In section 6.1.1.3, includes now a more detailed elaboration on the market launch measure including practical details that are taken to ensure legal certainty for innovators on the regulatory protection periods and a good faith approach. Moreover, the role of the Transparency Directive (also described in new Annex 14), national judicial control for abusive behaviour and a new subsection describing impact on prices of medicines has been added. The impact on price levels of this modulation is assessed in section 6.1.1.3. Reviewed and clarified use of standard and baseline protection periods throughout the report, where relevant.
(4) For the transferable exclusivity voucher proposed for AMR products, the report should clearly outline and analyse the key design parameters that affect its effectiveness and efficiency and the supporting evidence and benefit-cost analysis that will be necessary to trigger its practical application. Where trade-offs exist, these should be transparently presented. The report should clarify to what extent the transferable exclusivity voucher is expected to trigger the development of new medicines (not already having entered the development pipeline). It should better assess the impact on competition and prices on the relevant market of	In section 5.2.4, elaborated on transferable exclusivity voucher and its key design parameters. In section 6.1.1.4, clarified the impacts of the voucher, including the impact on generic/biosimilar competition from the use of the voucher, and elaborated on the benefit-cost analysis. In section 6.2, clarified that the transferable exclusivity voucher should encourage additional research to what is already in the pipeline.

the existing product chosen to benefit from the application of the voucher.	
(5) The report should be clear on who will benefit from the new measures and who will bear the costs and what the distributional impacts are for medicine developers, the pharma industry (including generics), SMEs, health care systems and patients.	In section 7.2, narrative adapted and tables added to clarify who benefits and who will bear cost from the measures and distributional impacts.
(6) The report should more thoroughly assess the overall impact of the measures promoting innovation and competitiveness of the EU pharmaceutical ecosystem, including SMEs. It should better assess how the reduced standard regulatory protection period will affect the long-term ecosystem innovation capacity. It should analyse how the measures will impact competition between companies (big pharma and SMEs), prices and affordability. It should anticipate unintended consequences on innovation and competitiveness and discuss the risk that the expected benefits will not materialise.	In sections 6.1.2-4 and 7.1, elaborated the impacts on competitiveness and SMEs. In section 6.1.1.2, added a subsection on RP reduction and impact on EU competitiveness. In section 7.5, addressed the limitations including the risk that the expected benefits will not materialise.
(7) The report should better compare the options, based on overall cost-benefit estimates for each option and each affected key group (including their presentation in consolidated comparison tables). It should be clear if a net positive benefit is expected as the preferred option shows a very low benefit-cost ratio.	In sections 7.2 and 8.1, tables added for clearer comparison of the options. The summary tables in these sections together with Annex 3 support the general finding that there is a positive benefit-cost ratio of the preferred option.

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 exact criteria and conditions of the voucher system to address antimicrobial resistance remain vague.	In section 5.2.4. (Policy Option C) on p.36 the paragraphs describing the "transferable exclusivity vouchers and restrictions on their granting and use" have been complemented with the exact award criteria to obtain a voucher.
The report is not sufficiently clear on the	Section 6.1.1.3 and notably the subsections

content, functioning and effectiveness of the envisaged safeguards which allows industry complying with the two year medicine launch requirement in all EU markets to benefit from extra-protection.	"*Practical details and impact of modulation of data protection for market launch (option C)"* and *"Would a decreased protection translate into price increase?" (p. 45-46)* have been revised and made clearer. We clarified that: • Non-action of the MS will be considered as tacit approval of the market launch conditions • SMEs and not-for-profit entities would receive a longer, 3-year period to comply • Comparison of international empirical data does not suggest a correlation between prices and data protection periods in different jurisdictions
The report should better assess the impacts of reduced regulatory protection periods on the sectors capacity to finance future innovations and international competitiveness.	A dedicated subsection on competitiveness and future innovation is added to section 8.1, on p. 68.

– *Evidence used together with sources and any issues regarding its quality*

The impact assessment and the accompanying evaluation have been built on:

- Evaluation of general pharmaceutical legislation (for the impact assessment)
- Participatory workshops bringing stakeholders together to inform respectively the evaluation and the impact assessment (see Annex 2: Stakeholder Consultation)
- In a back-to-back exercise, two studies were commissioned to a consortium led by Technopolis Group; an evaluation study and an impact assessment study. These studies are not publicly available and are annexed to this impact assessment as Annexes 12 and 13.

Extensive stakeholder consultations were organised, with input gathered through a public consultation, targeted surveys, an interview programme and workshops, for more information, see Annex 2: Stakeholder Consultation.

Evidence on costs were particularly difficult to gather. Public authorities and pharmaceutical industry provided very little information.

ANNEX 2: STAKEHOLDER CONSULTATION (SYNOPSIS REPORT)

1. Introduction

This report provides an overview of the stakeholder consultation activities carried out as part of the 'back-to-back' evaluation and impact assessment for the revision of the general pharmaceutical legislation (Directive 2001/83/EC and Regulation (EC) No 726/2004). 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 on potential future policy options.

Information was collected through consultations that took place between 30 March 2021 and 25 April 2022 and consisted of: feedback on the Commission combined evaluation roadmap/inception impact assessment (30 March-27 April 2021); Commission online public consultation (PC) (28 September-21 December 2021); targeted stakeholder surveys (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; and a validation workshop on the impact assessment findings (workshop 2), on 25 April 2022.

The following key stakeholder groups were identified as priority groups in the consultation strategy for the evaluation and revision of the legislation: Citizens; 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 National Medicines Authorities. Both actors play a pivotal role in the implementation of the pharmaceutical legislation. The Commission also worked with Member States, EEA countries (Iceland, Liechtenstein and Norway) and public authorities in the framework of the Pharmaceutical Committee[1]. Other national authorities were consulted to receive the point of view of payers or pricing and reimbursement (P&R) bodies in the meetings of the national authorities on Pricing, Reimbursement and Public Healthcare payers. The results of the consultation activities conducted for the Pharmaceutical strategy for Europe[2] were also considered as valuable inputs to the revision.

2. Methodology of the consultation activities

a) Feedback mechanism on Commission combined evaluation roadmap/inception impact assessment

The roadmap was published on the Commission *Have your Say*[3] website. 173 responses[4] were submitted by eleven types of stakeholders from 25 different countries. The largest number of submissions came from Belgium (34%), France (12%), Germany (8%) and the United States (7%). The large majority of submissions came from individual businesses (26%), CSOs (25,5%) and business associations (22,5%). All 173 entries were analysed in Excel and Word, recording the main

[1] Pharmaceutical Committee, Veterinary Pharmaceutical Committee and Expert groups (europa.eu)
[2] Pharmaceuticals – safe and affordable medicines (new EU strategy) (europa.eu)
[3] Revision of the EU general pharmaceuticals legislation (europa.eu)
[4] The full set of contributions received are published on the Commission website and can be found here: Revision of the EU general pharmaceuticals legislation (europa.eu).

topics, sub-topics and the type of stakeholder. No duplicates were found, but one campaign was identified from developers of innovative medicines.

b) Public consultation (PC)

The PC was published on the Commission *Have your Say*[5] website. There were 478 responses[6]. Most of the answers were submitted by respondents from Germany (18.2%), Belgium (16.7%), and France (9.2%). Contributions from non-EU countries mainly came from the United States (23%), United Kingdom (15%) and Switzerland (9%). With respect to the type of stakeholder groups, most respondents were from the pharmaceutical industry (28.4%), followed by patient or consumer organisations (13.8%), healthcare provider organisation (9.8%) and healthcare professionals (7.9%). 158 respondents (33.1%) attached 183 separate position documents and 19 (4%) did not provide any response to closed questions. The questionnaire was structured into two main sections, backward-looking questions (Questions 1 and 2) exploring how the legislation performed and which issues should be addressed by the revision of the legislation and forward-looking questions (Questions 3 to 15) addressing possible solutions to the problems identified. Closed questions were quantitatively analysed using Excel and STATA, while open questions were manually checked and opinions and themes were summarised for each stakeholder group. Campaigns were identified using combination of statistical analysis and manual checking in Excel.

Summary of campaigns:

Campaign 1 (Nuclear medicine practitioners – 23 answers) – main message: to adapt the legislation to facilitate production and marketing authorisation of radiopharmaceuticals and to simplify regulations for dispensing of radioactive medicinal products.

Campaign 2 (Wholesalers – 16 answers) – main message: to identify the causes of medicines shortages and address them; to revise the wholesale distribution licensing system and the distinction between pharmaceutical full-line wholesalers and other wholesalers; to recognise the role of pharmaceutical full-line wholesalers to address shortages and strengthen supply.

Campaign 3 (Innovative pharmaceutical industry – 12 answers) – main message: to consider the importance of a future-proof, predictable and stable legal framework and the importance of maintaining a good level of reimbursement and of regulatory protection periods.

Campaign 4 (Generic companies – 11 answers) – main message: to give incentives and facilitate the uptake of off-patent products, such as creating new regulatory pathways for value added medicines innovation.

Campaign 5 (Rare disease patient associations – 10 answers) – main message: to have better genetic testing for approval of oncology therapies; to ensure equal access to medicines and consider local capacity perspectives (i.e. hospital pharmacies); to use real-world evidence to generate information on access, patient needs and response to treatments.

[5] Revision of the EU general pharmaceuticals legislation (europa.eu)

[6] The full set of contributions received are published on the Commission and a report summarising the stakeholders' replies to the PC can also be found at: Revision of the EU general pharmaceuticals legislation (europa.eu)

Campaign 6 (Microbiome-based product developers – 10 answers) – main message: To integrate microbiome science in the legislation, including standards, methods and definitions.

c) Targeted stakeholder surveys (survey)

Surveys tailored for each stakeholder group were developed and implemented in the form of online questionnaires using the survey tool 'Survey Monkey'. It consisted of both closed (scored from 1 to 5) and open questions. Invitations to complete the survey were sent to 220 participants across all stakeholder groups. 90 of these organisations were asked to further disseminate the invitation through their networks. In total, 440 responses were received and 209 remained after cleaning and checking exercises. Representation amongst the different groups was not as anticipated with industry particularly over-represented (55.1%) and CSOs underrepresented (5,8%). Inputs were received from public authorities (26.4%), academic (8.2%) and health services (4.8%). Organisations from Western Europe (45.5%) mainly answered but contributions also came from Southern (19.7%), Eastern (16.3%) and Northern Europe (12.5%) and from non-EEA countries (6.3%). Data was downloaded and quantitatively analysed in STATA. Open-ended questions were analysed qualitatively in Excel. Eight campaigns were identified using a combination of statistical analysis and manual checking in Excel, but only three of them were considered for further analysis because they received more than ten responses.

Summary of campaigns:

Campaign 1 (Industry associations, parallel traders – 20 answers) – main message: support supply obligation for the marketing authorisation holder (MAH) at EU level to enable better competition of on-patent medicines, current legislation does not ensure sufficient stocks to enable a competitive parallel trade market to deliver on affordability; support increased move towards central authorisation for all medicines.

Campaign 2 (generic companies – 16 answers) – main message: burdensome regulatory requirements and inconsistency with other legal frameworks (medical device regulation, transparency directive…); support regulatory flexibility to accelerate access and avoid shortages; support stimulating the uptake of off-patent medicines and better dialogue between P&R authorities to improve access.

Campaign 3 (industry associations, wholesalers – 14 answers) – main message: current squeezes on margin/ remuneration for distribution endangers access to all medicines; support the regulatory flexibility applied during COVID-19 and the implementation of '*Green lanes'*.

d) Interviews

Semi-structured interviews of about one and an half hour were organised remotely via Zoom or Teams. They were based on an interview guide and individual questions were tailored to each interviewee. The guide had two parts covering the evaluation criteria and later discussing the problem analysis, possible policy measures and their comparison. A total of 138 individuals across all the identified stakeholder groups were interviewed including 57 representatives of the industry, 45 health service providers, 20 representatives of civil society organisations, 10 representatives of the public authorities and 6 academics. Summary notes were imported into Nvivo and coded thematically according to the objectives of the ongoing revision and abstracts were exported for synthesis into the reports.

e) Validation workshops

Two online stakeholder workshops were conducted with participants from all stakeholder groups. Both workshops followed the same structure: half-day event hosted via Zoom, with a plenary presentation and interactive polls, breakout sessions and plenary presentation of the breakout discussions. Ahead of the workshop, participants were able to choose two preferred breakout sessions and invitations included a discussion paper for contextualising the emerging findings. For both workshops, over 80% of participants were retained at the final plenary.

Validation workshop 1 on the evaluation findings

Out of the 246 invitations sent, 208 participants joined the workshop. The industry was the most represented group (86), followed by public authorities (61), civil society organisations (53), academics (23) and healthcare services (23). Five breakout rooms were created and grouped about 50 participants covering the five stakeholder 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.

Validation workshop 2 on the impact assessment findings

Out of the 339 invitations sent, 199 participants joined the workshop. Public authorities was the most represented group (82), followed by the industry (68), academics (17), civil society organisations (16), and healthcare services (11). Four breakout rooms were created and grouped about 50 participants covering the five stakeholder groups: 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.

3. Overview of responses

A summary of the main themes and views provided by each stakeholder group in during the consultation activities is presented below. With regards to the numerous consultation activities conducted, which covered simultaneously the evaluation and the impact assessment, it seemed natural to present the results according to topics and sub-topics.

a) Evaluation

Effectiveness

Overall, the stakeholders were positive about the effectiveness of the legislation and its revision in meeting its objectives, i.e. safeguarding public health in Europe and supporting innovation of new medicines, providing an attractive and robust authorisation system for medicines and ensuring quality and safety of medicines. The interviews also stressed the positive impact of the centralised procedure to achieve the objectives of the legislation. On innovation, the legislation delivers a good framework for biosimilar medicines and the PRIME scheme[7] has supported access to innovative products.

In some areas, the legislation was less effective; interviews with public authorities and healthcare professionals highlighted shortcomings in terms of ensuring access to medicines as reimbursement remains a Member State responsibility. Workshop 1 also identified the issue of access, affordability

[7] For details regarding the Priority Medicines Scheme, see EMA's website on PRIME

and innovation as areas where gaps remain to be addressed in the legislation. On access, several participants noted the lack of continuity in processes from marketing authorisation to patient access, with some products gaining marketing authorisation but not moving forward fast enough with the Member States' reimbursement decision. It was also suggested by some participants that regulatory protection can affect access by maintaining high prices for innovative medicines. In the scored questions of the survey, stakeholders indicated areas where the legislation has been effective to a lesser extent: *enabling access to affordable medicines for patients and health systems* (assessed as "moderate" by 33% CSOs, 15% public authorities and 24% academia), *minimising inefficiencies and administrative burden of regulatory procedures* (assessed as '*small'* by 30% industry and health services, 16% public authorities[8]), *enhancing security of supply of medicines and address shortages* (assessed as '*small*' by 24% industry, 42% CSOs, 16% public authorities and 23% health services), '*ensuring a competitive EU market for medicines'* (assessed as '*moderate*' by 24% industry, 8% CSOs and 35% public authorities), '*reducing the environmental footprint of medicines'* (assessed as '*very small*' by 16% industry, 25% CSOs, 20% public authorities).

In their answers to open questions to the PC, academics expressed concerns on the evidence requirements for certain innovative cancer medicines. HTA bodies, healthcare payer organisations and a regional authority were also concerned about quantification of benefits based on early efficacy assessment for their cost-effectiveness assessment. In the context of the functioning of the EU market, patient or consumer organisations, healthcare payers and generic/biosimilar companies indicated that the legislation did not facilitate generic entry sufficiently; a campaign by the latter group was identified. However, chemical industry respondents and innovative medicine companies opposed this position. Industry associations also shared the view that the current incentives of the legislation promote the development of traditional product types (e.g. small molecules), while members of the public authorities and CSOs noted the need for more incentives for medicines for rare diseases and new antimicrobials. Another issue raised in the PC and the interviews was the lack of flexibility to accommodate scientific advances, such as advanced therapy medicines (ATMPs) and real-world data; a view that was shared by academic, patient or consumer organisations, healthcare professionals and industry respondents.

Finally, during workshop 1 the environmental impact of pharmaceuticals and the environmental risk assessment (ERA) was debated. CSOs opposed industry stakeholders and shared concerns over the low priority of ERA in marketing authorisation decisions. The workshop also raised issues over genetically modified organisms (GMO) requirements, which do not fit with the legislation; complex innovative products lacking streamlined regulatory pathway; the lack of financial model for antimicrobials; the lack of incentives for repurposing and value-added medicines. Medicine shortages and security of supply were considered a high priority among participants and participants noted that lessons learned from the COVID-19 pandemic could prevent future shortages.

Efficiency

While 31% of the respondents to the survey indicated that the costs incurred by the legislation by all stakeholders impacted by it (industry and society including health systems and patients) were proportionate to its benefits to a moderate extent (46% industry, 8% CSOs, 15% public authorities, 18% academics and 30% health services), most stakeholders interviewed could not provide specific quantitative estimates of the costs and benefits associated with implementing the legislation. Interviews with industry stakeholders (41% of total interviews) noted the major drivers of costs were the additional data requirements related with the regulatory dossier and post-marketing authorisation

[8] For targeted surveys not all questions were asked to all stakeholders, e.g. this question was only answered by industry, public authorities and health services.

requirements. Both innovative and generic medicine companies stated that abolition of the recurrent 5-year renewal cycle reduced regulatory burden. Yet, several pharmaceutical industry respondents in the PC and in workshop 1 explained the impact of duplicative processes causes costly regulatory burden, hinders innovation, in particular for SMEs, and causes delays across the life cycle of medicines. Despite the challenges to provide accurate monetary costs, a few industry respondents to the survey provided one-off adjustment costs, related to upgrading IT systems, as well as ongoing regulatory costs. Public authorities noted in interviews and in the open questions of the PC that they had increased workload and resources, including staff numbers, due to the revised legislation.

Relevance

Interviews, workshop 1 and results from the survey showed a general consensus that the objectives of the legislation are still relevant, but that the legislation should be amended to address new technological developments, to provide more clarity over unmet medical needs (UMN) and to ensure access to affordable products. In interviews, stakeholders provided further details on the areas the legislation needs to medicines. Academics and CSOs raised issues related to the lack of robust evidence to allow reimbursement, CSOs and public authorities were also looking for more equitable access to medicines, CSOs and healthcare professionals stressed the need for incentives to address antimicrobial resistance (AMR) (for novel antimicrobials and environmental impact of antibiotics); CSOs, public authorities and healthcare professionals were looking for more initiatives to ensure security of supplies. These results were echoed by the survey, where these topics were all ranked as least relevant in the current legislation. In the survey, 24% of respondents assessed the legislation as '*very*' relevant to maintain the security of supply of medicines in the EU, 36% said it was '*moderately*' relevant to maintain resilience and responsiveness of health systems during health crises. For industry interviewees, the legislation needs to be flexible to allow for technological developments and borderline products, and expertise in areas such as gene therapy, healthcare digitisation and use of real-world evidence is important to be built in regulatory agencies. This view was also noted by public authority interviewees, though it was highlighted that resources are needed to continue to expand capacity and expertise.

Coherence

All consultation activities indicated there was no major issues concerning the internal coherence of the legislation. However, it was highlighted that coherence with other specialised legislation and wider EU policies (such as ATMPs, medical devices, GDPR and Blood, Tissue and Cells - BTC) could be improved. The lack of clarity of borderline products (e.g. medical devices containing medicines) was mentioned several times in interviews and in the PC by all stakeholders, noting that there is uncertainty over the legislation regulating the area of BTC and also concerns of excessive exclusivity given due to the interplay the legislation and the Orphan Regulation. The survey confirmed the same coherence problems but also highlighted the need to complement health-related legislations on GMOs (assessed as '*not at all'* coherent by 15% of stakeholders including 21% of industry and 5% of public authorities); to complement other EU legislations and policies on data protection (assessed as '*not at all'* coherent by 12% of stakeholders); on environmental requirements (assessed as '*slightly'* coherent by 12% of stakeholders including 12% of industry and 16% of public).

EU–added value

The EU-added value of the legislation was clearly supported among stakeholders interviewed compared to what can be achieved at the Member State level, in particular the benefit of the centralised authorisation procedure was noted as very valuable for small countries. This view was confirmed in workshop 1. The harmonisation of good manufacturing practices (GMP) and the regime of inspection was mentioned as another benefit of EU level action in workshop 1.

Participants noted, however, the tensions to maintain requirements for high safety and efficacy of medicines and to improve the speed of authorisation. All stakeholder groups interviewed agreed that EU level action was important to tackle the COVID-19 pandemic in a quicker and more coordinated way. This view was supported, in the survey, to a large or a very large extent. Overall, stakeholders agreed that EU level action has improved Member States ability to put in place appropriate measures. The results of the survey indicated that, without EU level action, Member States would have had no more than a '*very small*' (16% of respondents including 20% industry, 25% CSOs, 13% public authorities and 10% health services) to '*small' or 'moderate'* (24% of respondents including 26% industry, 33% CSOs, 18% public authorities and academics, 30% health services) ability to put in place appropriate measures.

b) Impact Assessment

The consultations indicated several areas of the legislation in which future policy measures may be needed. The following areas were discussed in details.

Incentives for innovation, including unmet medical needs and repurposing

The PC presented seven possible policy measures to support innovation, including for UMNs and repurposing. In the open-ended questions to the PC as well as in the survey, there was no consensus across stakeholder groups on the most appropriate types of incentives and regulatory schemes to support innovation. Industry stakeholders called for a robust, stable and predictable intellectual property and regulatory protection system to support innovation but there were internal disagreements within this group. A campaign led by innovative medicine companies to maintain current level of incentives and exploring new types of push and pull incentives. Another campaign led by generic/biosimilar companies stated that extending data/market protection for any medicine will have a significant negative impact on affordability and competitiveness. These opposing views were also echoed during interviews. Several industry respondents to the PC and interviewed also expressed a wish to increasing the current 1-year data protection for over-the-counter (OTC) switches to 3 years. Regional public authorities noted that an assessment for better definition of '*innovative medicines'* is needed, with transparency of research and development (R&D) costs as requirement for incentives, a view that was also supported by several CSOs in the PC. However, in interviews and workshop 2, industry stakeholders noted that transparency of R&D costs is not feasible as the methodology to calculate them would vary enormously and would contain sensitive information. Other regional public authorities stated that incentives for early market launch of generics and biosimilars could negatively impact medicine development and noted that strengthening the reward systems for innovative biotechnological medicines would be beneficial for UMN. Academics indicated a need for more incentives to engage universities, hospitals and other non-profit organisations to work in areas of low commercial interest.

The possibility to incentivise the provision of comparative data at the marketing authorisation stage was discussed in workshop 2. There was no consensus on whether there is a need or not for the provision of comparative data, with some noting that this data is already being provided where possible and also that, for some products, this would not be feasible (e.g. ATMPs).

There was broad agreement among stakeholders for the need to define UMN in a clear and transparent way including a multi-stakeholder approach to ensure consistency across different regulatory frameworks and along the medicine life cycle. The PC indicated the most important criteria to define UMN were the '*absence of satisfactory treatment authorised in the EU'* (scored as very important by 63% of all respondents) and the '*seriousness of a disease'* (scored as very important by 50% of all respondents). Similar positions were shared in workshop 2 with industry

stakeholders emphasising that the lack of a definition of UMN could lead to legal unpredictability and impact investment decisions. In the survey, CSOs and academics rated as favourable the option to '*reduce the regulatory protection period for new products that do not address an UMN*', while for industry, the most important measures were additional regulatory protection for repurposing and codification of the PRIME scheme. The majority of stakeholders, but the industry, were supportive of a measure to permit breaking of regulatory protection under exceptional circumstances and the simplification of the obligations for not-for-profit/non-commercial entities to become marketing authorisation holders (MAH). According to the industry this is because regulatory protection is crucial to incentivise the significant investment needed to develop medicines. Other concerns among workshop participants were raised about '*indication slicing'* to meet UMN and the inefficiency of the regulatory protection system due to the patent protection and supplementary protection certificates. In the PC, there was strong consensus across all stakeholder groups that '*early scientific support and faster review/authorisation of a new promising medicine for an UMN'* was a very important (50% of all answers)/ important measure (25% of all answers), and more so for SMEs. However, public authorities and healthcare professionals highlighted that expedited regulatory frameworks should include robust pharmacovigilance and post-marketing authorisation studies to address uncertainties, proposing that sanctions should be in place in case of non-compliance. During the interviews, public authorities confirmed the view that expedited authorisation is important but also cautioned that it should not compromise safety and efficacy of medicines. The PC also showed overall positive views across stakeholder groups on repurposing. Healthcare provider organisations and public authorities noted in the PC and in the interviews more efforts could be done to collect evidence of off-label use and using real-world evidence to identify repurposing studies. CSOs and learned societies suggested in interviews and the PC the creation of a database for repurposed medicine. Most respondents also supported the provision of financial rewards or incentives to stimulate repurposing, in particular for SMEs. Yet, HTA bodies cautioned in the PC that more regulatory or intellectual property protection would not have a positive result for patients, and fair pricing mechanisms should be used instead. This aspect was supported by several health service stakeholders in interviews. Despite this, industry stakeholders and especially generic and biosimilar companies interviewed noted that the current protection of the commercial value of repurposing efforts is a key limiting factor to progress in this area. Several interviewees noted that public investment could also play a role in repurposing as the research is often led by academics, hospital and other publicly funded institutions.

Antimicrobial resistance (AMR)

The survey presented ten possible policy measures to address AMR with the highest ranking measure being the '*introduction of a "pay or play" model'* mostly supported by CSOs and opposed by the industry as being unfair for companies with no expertise in AMR. The second highest ranking measure was '*additional market protection period for companies that hold MA for a novel antimicrobial'* mostly supported by the industry. However, there was low inter-stakeholder agreement for both measures. In the open-ended questions of the PC, there was similarly no clear consensus of opinions across stakeholder groups regarding the best types of regulatory incentives for the development of new antimicrobials. Several CSOs, public authorities, healthcare professionals and citizens cited small milestone rewards or longer data protection periods and novel incentives as potential positive measures facilitate development. Feedback from workshop 2 indicated stakeholders had mixed views on TEV. While large industry and SMEs see TEVs as an effective approach to meet the scale of the investment needed for sustainable R&D, the generic industry raised concerns about the high level of investment needed and the potential increase costs for the health system by delaying generic entry. Healthcare payers supported this last point. Interviews with public authorities highlighted that market exclusivity will not solve the problem, as the sale volumes

will remain too low to incentivise the required investment. Instead, they favoured direct financial incentives (e.g. market entry rewards). CSOs concurred that companies would profit from the TEV but recognised the system could be fine-tuned to meet the needs of the public.

Future-proofing: adapted, agile and predictable regulatory framework for novel products

In the PC, there was a consensus among stakeholders that *'creating adaptive regulatory frameworks for certain novel types of medicines or low volume products (hospital preparations) in coherence with other legal frameworks'* and *'making use of the possibility for 'regulatory sandboxes' in legislation to pilot certain categories of novel products/technologies'* are the most important measures to consider to create an adapted, agile and predictable regulatory framework for novel medicines, Both measures were ranked as '*very important*' by respectively 43% and 34% of all respondents. These results were also supported in the survey and in interviews, where stakeholders highlighted that regulatory sandbox could increase innovation, competition, and speed to market for complex /cutting edge medicinal products. However, CSOs were concerned that regulatory sandboxes have the potential to lead to undesirable consequences such as '*carve-outs'* and a '*two-tiered'* regulatory framework.

The majority of stakeholder groups also rated as '*very important*' (43% of all answers) or '*important*' (19% of all answers) the measure to '*introduce an EU-wide centrally coordinated process for early dialogue and more coordination among clinical trial, marketing authorisation, health technology assessment bodies, P&R authorities and payers for integrated medicines development and post-authorisation monitoring*'. While this view was supported in the survey across all stakeholder groups but academics, it should be noted that in the PC, the industry expressed split views with 28% of them considering this measure as '*not important'* and 37% as '*very important'*. Workshop 2 highlighted that a centralised classification mechanism would need to involve close stakeholder engagement and have good balance between the competence and expertise of the advisory bodies responsible under each legal framework.

In the survey, out of the three possible policy measures explored to assess the future-proofing aspects of the legislation; the measure to '*adapt the regulatory framework for certain categories of novel products and technologies, including personalised medicines, medicines that contain or consist of a GMOs, platform technologies, or combined with artificial intelligence*' scored consistently highest as having a positive or very positive impact by all stakeholders. The survey also proposed three policy measures related to scope and definitions of cell-based medicinal products. Overall, the measure '*adaptation of regulatory requirements for specific cell-based medicinal products (ATMPs) to facilitate production in the hospital setting while ensuring safety, quality and efficacy*' scored consistently highest as having a positive impact by stakeholders, except industry. The overall lowest ranked measure by the stakeholder groups was to '*provide a mechanism to exclude less complex cell-based medicinal products from the scope of the Pharmaceutical legislation and transfer to the BTC legislation*'. Workshop 2 highlighted that any changes to definitions require an integrated approach in consideration with other relevant legislations. Concerns were also raised about creating new classifications/categories for less-complex ATMPs and different regulatory routes for the different categories with the risk of causing confusion and jeopardise safety requirements for these products. Possible policy measures were also presented to harmonise requirements for GMOs Environmental Risk Assessment (ERA) where the measure to '*adapt a risk-based approach to determine when a specific ERA is required'* consistently scored highest. Interviews highlighted that this measure could increase the efficiency of authorisation of GMO-containing medicines and the competitiveness of the EU in this field.

Rewards and obligations related to improved access to medicines

In the PC, there was a shared view among all stakeholders that harmonisation of HTA and greater transparency on P&R is needed at the EU level to improve patient access to medicines. This view was confirmed during interviews and workshop 2. Stakeholders acknowledged that national policies on payment and reimbursement and reference price systems are outside the remit of the legislation and national competence. Among the eight measures explored to improve access in the PC, there was consensus among respondent on the least and most important measures to improve access. '*Maintain the current rules which provide no obligation to market medicines in all EU countries*' was scored as not important by 35% of the respondents, while '*introduce harmonised rules for multi-country packages of medicines*' scored as very important by 41% of all respondents with the strongest support coming from the industry (69%). Results from the survey confirm this view. The second highest rated measure was '*introduction of electronic product information (ePI)'* (scored very important by 27% of respondents). While the industry considered this measure as very important (47%), healthcare professionals, public authorities and citizens were relatively less supportive of this measure (13%). Workshop 2, dominated by industry stakeholders, also confirm this result. Participants explained that marketing authorisation could be complemented by ePI and multi-country packs to address the access issues related to national language requirements on leaflets and packaging. Healthcare professionals, CSOs and public authorities were concerned for citizens with no access to computers.

Regarding obligations to improve access, most consultation activities considered the *'requirement for companies to place – within a certain period after authorisation – a medicine on the market in the majority of Member States (including small markets)*' as a very important policy measure. Industry stakeholders were largely unsupportive of this measure and raised concerns about regulatory penalties to ensure medicine are available on the market. In their view, there are 'multifactorial' issues that may not be in their control, including differences in national regulatory requirements; speed of P&R negotiations; possibly of needing to conduct further research; and unforeseen manufacturing delays. These views were echoed in the interviews and the workshop 2. Results from the survey highlighted that the majority of stakeholders but industry were supportive of the '*requirement to MAH applying for mutual recognition procedure/decentralised procedure (MRP/DCP) to include small markets'*. The workshop 2 also discussed the obligation to place a centrally authorised medicine on the market in the majority of EU Member States. In general, participants found that the obligation could bring benefits depending on its implementation. It was suggested that the obligation could focus on facilitating access to early generic entry in countries where the obligation is not being met.

In the PC, there was consensus across most stakeholders groups that there should be new incentives for swift market launch of medicines across the EU: CSOs and academic/research institutes were most in favour (37% and 33%), with industry split between '*slightly important'* (27%, innovative pharmaceutical companies) and '*very important*' (31%, wholesalers). Results from the PC also indicated the measure to '*allow early introduction of generics in case of delayed market launch of medicines across the EU while respecting intellectual property rights'* was scored as '*very important'* by 30% of stakeholders to improve patient access to medicines. Workshop 2 also explored incentivising product launch in all EU Member States but participants were broadly of the view that the incentive will not necessarily ensure access but it could provide a financial incentive to launch in smaller markets. In the PC, there was a shared view among academics, healthcare professionals and CSOs for the introduction of a '*solidarity pricing'* whereby wealthy Member States contribute to create an '*EU based fund'* to finance access to medicines.

Enhance the competitive functioning of the market to ensure affordable medicines

The survey explored measures to enhance the competitive functioning of the market, including measures to support early market entry for off-patent medicines, to facilitate market entry of generics/biosimilars and to address 'duplicates' of centrally authorised medicines. Overall, the measures '*certification procedures to include outcomes that could be used for multiple products to avoid duplicative assessment*' and '*introduce new simpler regulatory pathway for generics and biosimilars to reduce assessment time by authorities*' were the most consistently highly scored by all stakeholder groups. The measure to '*establish the legal basis for EMA committee to provide advice on interchangeability of specific biologics*' was also highly scored by most stakeholder groups (29% of respondents assessed it as having a '*positive impact'*) but the industry. This group was split with 10% of respondents scoring the measure as '*strongly negative'*, 14% as having '*little or no impact'* and 12% with '*strongly positive impact*'.

The '*broadening of the scope of "Bolar exemption" beyond generics by allowing repurposing studies/comparative trials without infringing patent rights*' was assessed as having a '*positive impact*' by CSOs (25%), public authorities (31%) and academics (18%), The industry was relatively less supportive of this measure with 25% of respondents scoring it as having '*little or no impact*' and only 11% of respondents viewing is as having *'strong positive impact'*. Workshop 2, participants confirmed support for this measure in terms of broadening it to more actors and extending it to other purposes (e.g. repurposing studies or comparative studies). But there were mixed views about what aspects this measure should cover. The generic industry was supportive of extending the Bolar exemption. It was noted that the Bolar exemption needs to be considered along with the research exemption and that the activities exempted from patent infringement should be precisely defined. The generics industry noted that proposed changes do not cover all activities needed to get Day 1 launch.

One of the lowest ranked policy measure in the survey was '*introduce specific incentives for a limited number of first biosimilars for a shared market protection*', in particular by industry and public authorities. In workshop 2, it was discussed that this incentive is unlikely to increase uptake in smaller populations. Concerns were raised about giving only one product priority as this would limit competition and thus increase prices of medicines. Moreover, workshop participants indicated the bottleneck is the uptake rather than market entry of biosimilars. The industry shared in interviews concerns over the incompatibility of shared market protection with EU regulatory system because of patent linkage issues. While CSOs (49%), citizens (39%), academics (33%) and public authorities (22%) considered this measure as very important, 26% of the industry ranked it as '*not important'*. In interviews, innovative medicine companies indicated their concerns that increasing incentives for generic entry to the market could discourage innovation in EU.

Security and supply of medicines

The PC presented ten possible policy measures to ensure security of supply of medicines in the EU. Overall, stakeholders scored the measure '*companies to have shortage prevention plans'* (46%) and '*introduce a shortage monitoring system at EU level'* (43%) as very important. In contrast, '*maintaining the current rules*' (15%) and '*introducing penalties for non-compliance by companies with proposed new obligations*' (18%) were scored as the least important. CSOs (34%) and public authorities (30%) ranked as very important the requirement for companies to diversify their supply chains, while 34% of industry considered this as not important. 41% of stakeholders ranked as very important '*monitoring and reporting of medicines shortages coordinated at the EU level*' as another measure to ensure security of supply. This view was confirmed in the survey, where the highest

ranked policy measure was the '*introduction of an EU information exchange on critical shortages based on national supply-demand monitoring data'*.

In workshop 2, stakeholders explained that diversification of the supply chain is challenging and not always feasible due to the difficulty to find alternative suppliers upstream in the supply chain. It was pointed out that having a more diverse and sustainable supply chain would likely increase the cost of medicines due to increased compliance costs.

On the possibility to increase shortage notification requirements for all medicines from 2 to 6 months, workshop participants suggested having a definition for critical shortage rather than increasing the notification period. The industry consistently supported this view in interviews and in the PC. In the workshop, concerns were also raised that earlier notification of potential shortages could lead to real shortages by triggering stockpiling and hoarding in Member States. In the PC and in interviews, several public authorities explained that the current notification requirements are appropriate, but compliance needs to be improved. According to academics a requirement for safety stocks should not result in significant price rises. In the survey, most stakeholders, but wholesalers and the developers, thought the measure to '*require MAH to notify authorities of impending shortages 6 months in advance*' would positively impact the security of supply. This split view was also confirmed in the PC.

The issue of stockpiling measures, requirements (or reserve requirements) for MAHs and wholesalers for critical medicines was discussed at the workshop. It was assessed by most participants as an effective approach to temporarily alleviate the effects of shortages. However, such measure would need to happen at the EU level in the form of unfinished product, and for critical medicines only. When considering EU-wide vs national level stockpiling, it was suggested that implementation at a national level would require an obligation for stock-sharing and special flexibility to facilitate easy movement of products between Member States. On the duration of stockpiling, there was a consensus that this could not be a permanent solution but only helpful for the first 2-3 weeks of shortages. Participants highlighted warehousing requirements for stockpiling would be challenging for certain types of products that need to be produced on site or cannot be stored for long periods of time (e.g. plasma-derived products or personalised medicines).

Quality and manufacturing

Several policy options were discussed in the consultation activities including harmonising a system of sanctions on GMP, increase sustainability performance in relation to AMR, ensure the legislation is adapted to regulate new manufacturing methods and, lastly, the modification of inspections regime and supply chain oversight. In the survey, only public authorities and industry stakeholders contributed to these aspects. Public authorities viewed all policies, on average, as having potential for positive or large positive impact. Industry stakeholders were in support of reinforcing Member States' GMP and good distribution practices (GDP) inspection capacity by setting up a joint audit scheme to reinforce and strengthen the quality of inspections; strengthening the role of the EMA in supporting the robust oversight of manufacturing sites and in the coordination of all inspections; and to adapt the terms of the legislation to accommodate new and emerging manufacturing methods. They were less in favour of introducing a harmonised system of sanctions related to GMP and GDP; of extending the scope of mandatory inspections to encompass supply chains; of increasing the responsibilities of MAH vis-a-vis the quality of the supply of APIs and raw materials and clarify responsibilities of business operators over the entire supply chain; of adapting GMP procedures to environmental and antimicrobials challenges. Interviews confirmed the support for the policies mentioned above, but also highlighted some tensions. National competent authorities noted the need for more resources to train inspectors (e.g. in the area of antimicrobial resistance) and to cope with

an increased regime of inspections. Industry stakeholders noted that the system of sanctions and the increased regime of inspection and supply chain oversight would present barriers for SMEs. They also stressed the existence of other legislations regulating antimicrobials and thus on the risk for duplication. The PC confirmed the overall positive view on the need to adapt new manufacturing rules and methods. In open questions, CSOs, academics, health services and citizens highlighted the importance to increase the transparency of the supply chain through more oversight. Regional public authorities suggested to increase cooperation for supply chain monitoring within and outside the EU; to clarify the documentation necessary for active substances production; to promote EU manufacturing of essential vaccines and medicines. Both pharmaceutical industry and pharmaceuticals traders/wholesalers emphasised the need for more resources for GMP inspections in less regulated third countries to ensure a level playing field.

Environmental challenges

The PC showed general consensus on the importance of strengthening efforts to reduce the environmental impact of medicines, but opinions varied on the urgency and appropriate measures. Citizens were concerned about the pollution of waters, the environmental impact of packaging and disposal of medicines. Environmental organisations expressed that the ERA should be a requirement and part of the risk-benefit analysis for all medicines and through the whole life cycle of the product, including assessment for AMR. This position was also expressed during workshop 1, where CSOs opposed industry stakeholders and shared concerns over the low priority of ERA in marketing authorisation decisions. Several public authorities, healthcare professionals and CSOs suggested the inclusion of environmental impact in the decision-making criteria to award incentives to developers and reduce the environmental impact of medicines. Pharmaceutical industry noted in the PC and in interviews that most APIs do not have a significant risk for the environment and that ERA for off-patent medicines are duplicative and unnecessary. The chemicals industry noted that the current system for tendering does not reward environmentally sound manufacturing practices, and instead focus on low prices. In their view, environmental standards could benefit from more international regulatory alignment. Industry respondents suggested the creation of a fund for investment in greener manufacturing practices in the EU to help SMEs and improve security of supply. Several environmental organisations, healthcare professionals, civils society organisations and citizens noted in the PC the need for clearer guidelines for procurement of medicines, which should include greener manufacturing practices, and more MAH responsibility over all supply chain actors.

Of the three possible policy measures presented in the survey, the option '*to strengthen the environmental risk assessment (ERA) requirements and conditions of use for medicines*' was rated positively by most public authorities, healthcare professionals and CSOs, while the industry was divided with answers ranging from strong negative to strong positive impact. There was no consensus within academics on this option. The option '*to introduce a requirement to include information on the environmental risk of manufacturing medicines, including supply chain actors, in ERA / application dossiers'* was mostly rated as negative by industry stakeholders while all other stakeholder groups viewed this option bringing a positive impact. The last option of the survey '*to establish an advisory role for EMA with regard to ERA and green manufacturing aspects and quality of medicines*' was seen as a having potential positive impact for all stakeholder groups, with only industry average response closer to '*little to no impact*'.

Interviews with industry stakeholders noted that higher manufacturing standards to reduce environmental impact comes with associated costs. In this regard, EU companies should be supported to remain competitive with other regions. Public authorities also highlighted the double challenge to ensure environmental sustainability and to bring manufacturing back to Europe. This will require a multifactorial approach beyond the legislation. They also confirmed an overall support

for strengthening the ERA as long as it does not impact access to patients. CSOs stressed the need for transparency over environmental impact of medicines and suggested to make use of the best practices already implemented across Member States. Workshop 2 confirmed the general view that there is a tension between the need to reduce regulatory burden while expanding environmental considerations. There was a general consensus that the legislation should be linked to environmental legislations. Participants raised several issues, e.g. inspectorates lacking adequate background or mandate over environmental matters, environmental parameters not fit for purpose for GMP and environmental risks related to manufacturing can be site specific and difficult to standardise.

COVID-19 lessons learnt

Participants of workshop 1 highlighted that medicine shortages and security of supply was a high priority and noted that lessons learned from the COVID-19 pandemic could prevent future shortages. Out of the four possible policy measures of the survey, the '*possibility of introducing a codified system of rolling reviews for products addressing UMN'* did not gain stakeholders consensus, with industry and public authorities rating this option more favourable than health services and academics. In interviews, all stakeholders recognised that the rolling reviews were successful to address the pandemic. Some public authorities noted the benefit of more developer-regulator interaction but others also highlighted the unsustainability of that system for national authorities. CSOs and healthcare services also noted that if P&R authorities are not able to assess therapeutic value (due to lack of relevant data), the medicine will not reach patients. In the PC, this view was confirmed by academics, healthcare payers and CSOs respondents. Yet, several pharmaceutical industry respondents argued that real-world evidence can support data provision and rolling reviews can play an important role for certain products (e.g. plasma-derived medicinal products). Similar exchanges took place during workshop 1. Academics interviewed noted that the EMA pandemic taskforce was a key enabler in allowing coordinated response and CSOs, healthcare professionals and public authorities discussed the importance of the EU joint procurement of vaccines for speedy and efficient action for access. Industry stakeholders interviewed noted that the virtual audits and inspections could be implemented post-pandemic to save resources, and they highlighted the need for more alignment in clinical trials during pandemics to ensure speed and appropriate designs. It was also noted that the GMO exemption for COVID-19 vaccine could be applied to other areas, such as low risk ATMPs. Public authorities also noted that transparency measures were implemented as a response to the pandemic, as well as strengthening of the network (national competent authorities, EMA and the Commission) through regular meetings, which brought positive outcomes.

The second measure of the survey, '*the possibility of allowing regulators to reject immature marketing authorisation applications'* (when data is insufficient to conduct full assessment to support a decision) was rated as having strong positive impact by public authorities, while industry rated it more negatively. The third measure *to establish an EU emergency use authorisation (EUA) of medicines* received an overall positive score by all stakeholders as currently, there is only national emergency authorisation. The last and similar measure, '*to establish an EUA that would still leave Member States to decide but it would be based on EU level scientific advice'* was also positively viewed by all stakeholder groups, except for academics who ranked it as having little or no impact. Neither the third, nor the fourth measure were discussed in the PC, apart from two pharmaceutical industry respondents expressing a positive view on an EU EUA.

ANNEX 3: WHO IS AFFECTED AND HOW?

1. Practical implications of the initiative

The proposed revisions have substantial positive implications for EU patients, companies and national health systems.

For **patients**, there are many improvements foreseen in all areas of importance: improving the flow of cutting-edge treatments available for conditions for which there are no effective treatment options currently (UMNs), 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 also support environmental goals. Measures on security of supply will moreover improve access to medicines.

For **companies,** the proposed revisions seek to strike a balance between ensuring a strongly positive environment for research-intensive pharma industry to continue to develop its cutting-edge products within the EU and the need to ensure all EU member states and citizens have access to a broader array of treatment options. Therefore, the modulated incentive scheme provides attractive incentives for innovation and placing on the market. The future proofing of the regulatory framework will also embrace technological change. New obligations for shortages prevention and environmental protection will result in additional costs for businesses. However, simplification and long term benefits from digitalisation are likely to offset any new costs and result in earlier authorisations.

For **health systems**, public health budgets would also benefit from the modulated incentive scheme since more EU citizens will have access to treatments, which results in savings due to more effective treatment and reduced hospitalisations. They will also benefit from stronger competition and transparency measures around public funding for clinical trials. There would be additional societal benefits for families and carers too, in terms of both quality of life / independence and earning potential. Overall, the new incentives will come with costs for healthcare budgets but the public health benefits should outweigh those.

For **regulators**, the effects of the proposed changes would be overall positive especially due to various horizontal measures, which will allow to better coordinate, simplify and accelerate regulatory processes to the benefit of industry and launch new digitalisation programmes to improve the integration and efficiency of the regulatory system overall (as well as its interfaces with other regulatory systems).

2. Summary of costs and benefits

Table I presents an overview of the estimated benefits for the pivotal measures under the preferred option, and Table II presents an overview of the main estimated costs associated with those measures.

The estimate of benefits is an **underestimate as there will be many indirect benefits for health systems and patients from improved access to new medicines for UMNs, new classes of antimicrobials and extended market access**. However, while we expect many tens of thousands of individual citizens to benefit in some degree from these revisions, it has not been possible to establish quantify and monetise these many and various social impacts. Likewise, the estimate of costs is also an underestimate as several costs could not be quantified.

For the market access, the overviews include benefits and costs for only the variant of the market launch measure with one year of conditional protection for launch in all Member States within 2 years.

Benefits

For **patients**, the principal benefit would be access to new medicines. The measures proposed would provide access to new medicines to 67 million more (as compared to today) EU citizens, should they need them.

For **companies**, the principal direct benefits relate to the gross profits for originators and generic/biosimilar companies associated with additional flow of protected sales that will result from the various incentives foreseen (e.g. a year one extension to the overall period of regulatory data protection for medicines addressing an unmet medical need).

For **health systems**, the main indirect benefits relate to the lower prices for health payers associated with those medicines where MA holders do not place their product in all Members States and where, as a consequence, generic competition will emerge two or one years earlier.

There are also savings expected from the various horizontal measures, which will allow benefits for both companies and **regulators**. They will allow to better coordinate, simplify and accelerate regulatory processes to the benefit of industry and launch new digitalisation programmes to improve the integration and efficiency of the regulatory system overall (as well as its interfaces with other regulatory systems). Quantified benefits from the horizontal measure are for companies in the range of €35-70m annually and for regulators €102.3-204m.

I. Overview of Benefits (total for all provisions) – Preferred Option		
Description	***Amount***	***Comments***
Direct benefits		
Medicines for unmet medical needs (UMNs)	On average, additional **3 new medicines annually** relevant to UMNs (c. 45 new medicines over 15 years). This would result in **originators** securing an additional **€282m** gross profit sales annually (15 years: €4.23bn).	+12 months extension of RDP for innovation, particularly around unmet medical needs (UMNs) would result in a higher proportion of UMNs within all newly authorised medicines. While 1-2 additional UMN medicines are expected annually, the extension of the RDP is expected to apply to 3 UMN medicines annually.
Novel antimicrobials	An additional **1 novel antimicrobial annually** (c. 15 over 15 years). This would result in **originators** securing an additional **€387m** gross profit annually (15 years: €5.8bn).	The transferable voucher, if approved, would provide strong support for innovation in novel antimicrobials. The additional income may be secured by the developer of the novel antimicrobial where they use a voucher with another high value medicine in their portfolio or split between the developer of the antimicrobial and another originator that has purchased the (transferable) voucher. We have estimated the purchase value at €360m (assuming one voucher a year). With more breakthroughs a more vouchers the average sale price would fall.
Comparative trials	A small number of EMA medicines applications will be able to implement more robust trials and take advantage of the incentive (**8 a**	+6 months extension of RDP for medicines applications that include

I. Overview of Benefits (total for all provisions) – Preferred Option		
Description	***Amount***	***Comments***
	year). This would result in **originators** securing an additional **€378m** gross profit annually (15 years: €5.7bn).	the findings of comparative trials.
Market access	The great majority of new medicines will be able to comply with the market access conditions. **8 medicines annually** (120 over 15 years) may fail to meet the conditions, and in these cases the RDP will lapse at 6+2 years (not 6+2+1). For this sub-set of products where the RDP is the last line of defence, there will be a **€384m** gain each year (€5.7bn over 15 years) to the **EU health system and patients**, because of lower prices from earlier competition by generics. **Generic companies** would secure an additional **€51m** annually in gross profits (€765m over 15 years).	+1 years protection conditional on launch in all EU markets in 2 years (the variant).
1 year general reduction of the RP	The reduced protection would allow earlier generic entry and price competition, and also the lower prices would increase patients' access to medicines. **Health system and patients** will gain **€1,008m** a year (€15.1bn over 15 years), and **generic companies** would secure an additional **€113m** per year (€2bn over 15 years).	
Indirect benefits		
Patients benefit from effective medicines (UMNs)	Thousands of EU citizens will have access to treatments that help recover them from or manage their debilitating conditions, improving their quality of life and life expectancy. There may also be indirect benefits / savings for health systems from more effective treatment and reduced hospitalisations. There would be benefits for families and carers too, in terms of both quality of life / independence and earning potential.	It is not possible to quantify / monetise (indirect) patient benefits given the diversity of UMNs (certain neurological conditions, cancers, muscular dystrophy, etc.). These conditions may affect hundreds of citizens or millions in the case of Alzheimer.
Patients have access to new classes of antimicrobials that help to contain AMR	It is estimated that each year about 670,000 infections occur, and that 33,000 Europeans die as a consequence of antibiotic-resistant bacteria with the burden being highest in the elderly and infants. It is also estimated that AMR costs the EU €1.5bn per year in healthcare costs and productivity losses. Even a 1% improvement in our management of AMR could save several hundred lives annually and save health systems hundreds of millions too.	It was not possible to quantify / monetise the (indirect) patient benefits that might result from new classes of antimicrobials.
Improved decision making for HTAs / Reimbursement bodies	More robust evidence from comparative trials should facilitate HTA decision making, leading to improved reimbursement decisions and faster decisions / access where medicines are approved for reimbursement.	It was not possible to quantify / monetise the (indirect) HTA and patient benefits that might result from the greater use of more robust trials.
All EU member states (inc smaller countries) have improved access to new medicines	On average, new medicines will be available to patients in 22-25 markets compared with the current situation (12-15), reaching 80% of the population compared with the current situation (c. 65%). The access to all new medicines in 5-10 additional markets will mean that hundreds of thousands of EU citizens will have better treatment options, with accompanying improvements in health equality and possibly public health.	It was not possible to quantify / monetise the (indirect) patient benefits that might result from the systematic extension of market access
Improved management of shortages	Most EU countries report increasing numbers of medicine shortages, with the great majority having recorded shortages for 200 or more medicines in the year. Fewer shortages may benefit tens of thousands of patients, with access to the more appropriate medicines. According to the Pharmaceutical Group of the EU, eliminating shortages might save healthcare systems 5-10% of their pharmacy-related staff costs as well as time wasted by frontline staff.	Fewer shortages would mean more patients have access to the medicines they need. Healthcare systems would see cost savings from avoiding time wasted deciding / finding appropriate alternative medicines.
Improved environmental performance of pharma industry	This may make a positive difference to 40-50 new medicines a year (600-750 in 15 years). This should result in a reduction in the intrinsic environmental risks of	New medicines would be subject to a more rigorous assessment, which should feed forward to more

I. Overview of Benefits (total for all provisions) – Preferred Option		
Description	***Amount***	***Comments***
	a proportion of medicines, a lowering of the levels of active ingredients getting into the environment through excretion and a lowering of the level and number of accidental releases to the environment by manufacturers (mostly non-EU).	informed selection of APIs, encourage green pharma and select for higher standards across global supply chains.
Administrative cost savings related to the 'one in, one out' approach*		
Streamlining, acceleration of processes and coordination of network	**Businesses** should realise savings in the range **€15m-€30m annually** (€225m-€450m over 15 years). European and national **regulators** should see savings in the range **€33.5m-€67m annually** (€502.5m-€1005m over 15 years). Overall savings should represent on average **€72.75m annually** (€1.09bn over 15 years).	Businesses will benefit from various simplification and governance enhancements producing administrative cost savings. European and national regulators should see a reduction in duplication of effort across committees and among regulators, producing savings in enforcement costs
Digitalisation	Digitalisation savings for **businesses** in the range **€7.5m-€15m annually** (€112.5m-€225m over 15 years). Digitalisation savings for **regulators** in the range **€67m-€134m annually** (€1,005m-€2,010m over 15 years). Overall savings of on average **€112m annually** (€1.68bn over 15 years)	The various digital initiatives proposed will save time and administrative costs for businesses and deliver substantial efficiencies / reductions in enforcement costs for regulators.
Adaptations to new concepts and support SMEs and non-commercial organisations	Enhancement savings for **businesses** in the range **€7.5m-€15m annually** (€112.5m-€225m over 15 years). Enhancement indirect benefits for **businesses** in the range **€5m-€10m annually** (€75m-€150m over 15 years). Enhancement savings for **regulators** in the range **€1.75m-€3.5m annually** (€26.25m-€52.5m over 15 years). Overall savings of on average **€21m annually** (€321mn over 15 years).	Industry - and SMEs in particular - should benefit from better and more dynamic advice avoiding queries on applications (delay) and rework to the same (cost); regulators should benefit from more mature applications that can be assessed more easily and quickly. There may be some limited indirect benefits, whereby faster assessments, on average, may facilitate at least some new medicines being approved for sale earlier and some generics entering the market earlier.

(1) 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) We indicate which stakeholder group is the main recipient of the benefit in the comment section;(3) For reductions in regulatory costs, we describe how the saving arises (e.g. reductions in administrative costs, regulatory charges, enforcement costs, etc.;)

Costs

For **patients**, the principal costs (indirect) will relate to reduced access to treatments associated with the additional delays in generic entry for new medicines that have benefitted from extensions.

The principal costs for **industry** are associated with the reduced general RP protection, implementation of market access conditions and conduct of comparative clinical trials. In addition costs for industry in relation to reporting on shortages and environmental risks and enhanced support in the range of €31.6m-47.4m annually.

The principal costs for **health systems** relate to the additional period in which they will need to pay a premium price for medicines benefiting from any extensions to the period of regulatory data protection.

For **regulators**, they would bear some costs relating to the design and implementation of the wide-ranging proposals for streamlining and digitalisation as well as shortages, strengthened

environmental risk assessment and enhanced support. Their costs would be in the range of €92.3-189.7m annually plus one-off costs of €136.8-383.6m.

II. Overview of costs – Preferred option							
		Citizens/Consumers		**Businesses**		**Administrations**	
		One-off	**Recurrent**	**One-off**	**Recurrent**	**One-off**	**Recurrent**
UMNs	Direct adjustment costs						
	Direct administrative costs						
	Direct regulatory fees and charges						
	Direct enforcement costs						
	Indirect costs		Costs for 'unserved' patients €246m a year €3.69bn over 15 years		Lost gross profits for generics €39m a year €585m over 15 years		Additional costs for payers €162m a year €2.43bn over 15 years
AMR	Direct adjustment costs				E.g. industry would incur costs for the development of AMR lifecycle monitoring plans; these cost could not be quantified.		E.g. regulators would incur costs to examine the AMR lifecycle monitoring plans; these costs could not be quantified.
	Direct administrative costs						
	Direct regulatory fees and charges						
	Direct enforcement costs						
	Indirect costs		Costs for 'unserved' patients €158m a year €2.37bn over 15 years		Lost gross profits for generics €54m a year €360m over 15 years		Additional costs for payers €283m a year €4.2bn over 15 years
Comparative trials	Direct adjustment costs				Comparative trials conducted by originator €280m a year €4.2bn over 15 years		
	Direct administrative costs						
	Direct regulatory fees and charges						
	Direct enforcement costs						
	Indirect costs		Costs for		Lost gross		Additional

II. Overview of costs – Preferred option							
		Citizens/Consumers		Businesses		Administrations	
		One-off	Recurrent	One-off	Recurrent	One-off	Recurrent
			'unserved' patients €112m a year €1.68bn over 15 years		profits for generics €52m a year €780m over 15 years		costs for payers €218m a year €3.27bn over 15 years
Market access (variant with one year protection)	Direct adjustment costs						
	Direct administrative costs				Requesting confirmations of supply to obtain extension of RP; costs not quantified. More applications for P&R; costs not quantified.		Confirmation of supply by MS; costs not quantified.
	Direct regulatory fees and charges						
	Direct enforcement costs						
	Indirect costs				Lost gross profits originators €378m a year €5.6bn over 15 years		P&R bodies to decide on more applications; costs not quantified.
1 year general reduction of RP	Direct adjustment costs						
	Direct administrative costs						
	Direct regulatory fees and charges						
	Direct enforcement costs						
	Indirect costs				€991m gross profit reduction for originators €14.9bn over 15 years		
Shortages	Direct adjustment costs						
	Direct administrative costs				Additional costs for industry €10m-€20m a year (ave €15m) €150m-€300m over 15 years (ave €225m)		
	Direct regulatory fees and charges						
	Direct enforcement costs						Additional costs for

II. Overview of costs – Preferred option							
		Citizens/Consumers		Businesses		Administrations	
		One-off	Recurrent	One-off	Recurrent	One-off	Recurrent
							regulators €10m-€20m a year (ave €15m) €150m-€300m over 15 years (ave €225m)
	Indirect costs						
Environment	Direct adjustment costs						
	Direct administrative costs				Additional costs for industry €20m-€25m a year (ave €22.5m) €300m-€375m over 15 years (ave €337.5m)		
	Direct regulatory fees and charges						
	Direct enforcement costs						Additional costs for regulators €20m-€25m a year (ave €22.5m) €300m-€375m over 15 years (ave €337.5m)
	Indirect costs						
Streamlining	Direct adjustment costs						
	Direct administrative costs						
	Direct regulatory fees and charges						
	Direct enforcement costs					Additional one-off costs for regulators €16.8m-€33.6m (ave €25.2m)	Additional costs for regulators €33.5m-€67.5m a year (ave €50.5m) €502.5m-€1.01bn over 15 years (ave €757.5m)
	Indirect costs						
Digitalisation	Direct adjustment costs						
	Direct administrative costs						

II. Overview of costs – Preferred option							
		Citizens/Consumers		**Businesses**		**Administrations**	
		One-off	**Recurrent**	**One-off**	**Recurrent**	**One-off**	**Recurrent**
	Direct regulatory fees and charges						
	Direct enforcement costs					Additional one-off costs for regulators €120m-€350m (ave €235m)	Additional costs for regulators €24m-€70m a year (ave €47m) €360m-€1.05bn over 15 years (ave €705m)
	Indirect costs						
Enhanced support	Direct adjustment costs						
	Direct administrative costs						
	Direct regulatory fees and charges						
	Direct enforcement costs						Additional costs for regulators €4.8m-€7.2m a year (ave €6m) €72m-€108m over 15 years (ave €90m)
	Indirect costs				Additional costs for industry for engaging with regulators €1.6m-€2.4m a year (ave €2m) €24m-€36m over 15 years (ave €30m)		
Costs related to the 'one in, one out' approach							
Total	Direct adjustment costs						
	Indirect adjustment costs						
	Administrative costs (for offsetting)				Administrative costs to businesses €37.5m a year €562.5m over 15 years		

(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.

3. Relevant sustainable development goals

III. Overview of relevant Sustainable Development Goals – Preferred Option(s)		
Relevant SDG	**Expected progress towards the Goal**	**Comments**
SDG 3: Good Health and Well-Being for people Highly relevant	The revision will help futureproof the legislation, continuing to safeguard public health. The revisions will increase the proportion of new medicines that address unmet medical needs (UMN), thereby creating the potential for millions of people across the EU and internationally to access effective treatments for their debilitating conditions. The revisions will introduce new incentives for innovative with the potential to tackle disease resistant pathogens and contribute to managing antimicrobials resistance (AMR).	The expected progress towards SDG 3 and SDG 9 are closely interlinked and complementary. By improving the innovation capacity of the EU pharmaceutical industry, the revision will contribute to improve the access to all treatment for all Europeans and therefore to ensure good health and well-being to European citizens.
SDG 9: Industry, Innovation, and Infrastructure. Highly relevant	The revision sought to simultaneously support the EU pharmaceutical industry and patients. The introduction of substantial additional incentives for major medicines innovations in the areas of UMNs, AMRs and other therapeutic areas where there is an evident social need and a demonstrable market failure (e.g. difficult / costly science and small, volatile markets). The revision should strengthen the EU industry's global competitiveness in those areas most directly related to UMNs. The revisions is expected to lead to a refocus of the R&D industry on European territory attracted by streamlined and harmonised regulatory environments. Thus, the revision should also contribute to the strengthening of EU's attractiveness as a place for carrying out medicines research globally, through the implementation of new incentives for innovation, new definitions, various streamlining and digitalisation measures. The revision is expected to strengthen the EU generic industry's competitiveness by incentivising the industry stakeholder to retain their manufacturing capacity within the EU. The support ensured to the overall pharmaceutical industry and the related impact is expected to be extended to SMEs as well. However measures such as the transferable vouchers may provide a good opportunity for small biotech firms working on novel antimicrobials to secure substantial additional funding for research through the sale of vouchers or the raising of new finance or acquisition. The proposals to make the regulatory and scientific advice more dynamic and interactive is likely to be valuable to SMEs.	The revision will support progress towards SDG 9 by creating a future-proof environment supporting the pharmaceutical industry. Measures addressing the inefficiencies of the regulatory system such as the streamlining of administrative and regulatory activities; the adaptation to innovation and digitalisation will largely contribute to enhance support of the industry. Those measures are expected to ease innovation and day-to-day activities for all industry stakeholders, all along the lifecycle of medicines.
SDG 10: Reduced Inequalities Relevant	The revision will support improvements in health equality through improved market access, increasing the number and speed at which new medicines are launched on the great majority of EU markets. The revision will also support improvements in the management of medicines shortages across the EU, thus helping to contain the upward trend in shortages and increasing the likelihood that patients receive the most suitable medicines. Finally, the increase in the proportion of medicines addressing unmet medical needs will provide those patients with treatment options where that is not the case currently. Moreover, it should be noted that: - The revision of general pharmaceutical legislation aligns with the pharmaceutical strategy for Europe, which emphasises the need to ensure access to safe, high quality and effective medicines as a key element of social well-being, including for persons from disadvantaged, vulnerable groups, such as people with disabilities, people with a minority ethnic or racial background and older people. - The revision of the general pharmaceutical legislation aligns with the revision of the orphan and paediatric legislation focusing on reducing health inequalities for these specific population.	Progresses towards SDG 10 echoed the ones of SDG 3. Measures such as innovation in the areas of UMNs, AMR and the improvement of market access conditions are expected to contribute to the reduction of inequalities within the entire European population.

ANNEX 4: ANALYTICAL METHODS

Methodology and models for the Impact Assessment

1. Data sources

There have been multiple data sources and related analytical methods applied to provide evidence for the impact assessment of the policy elements and options in this study.

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.

Our search strategy followed a heuristic approach, using the objectives of the revision to focus our efforts, but building out from our existing view of matters, based on our and others' recent studies, but also the Commission's own recommendations. Our searches covered peer-reviewed and grey literature using keywords in English, Dutch, French, German and Spanish across Pubmed, Scopus, EU institutions, agencies and regulator websites, Google Scholar and international organisations such as WHO and OECD. We have also identified sources from stakeholders such as industry organisations and patient associations.

Comparative legal analysis: we explored pharmaceutical legislation of third country jurisdictions in areas where a revision was proposed in the EU. These were based on desk research complemented as needed by targeted interviews with national experts. The following seven countries were selected: USA, Canada, Australia, South Korea, China, Japan, Israel – covering a mix of major developed global markets and smaller ones where regulatory innovation was expected. We have used a standard country report template as data gathering and reporting tool. Sources for those reports included legal research on the third country legal systems but also literature review both in English and respective national languages on the workability and outcome of these legal systems and interviews with relevant actors in these countries (i.e. competent authorities and experts).

Country reports were completed by national experts with good understandings of the national context and relevant language skills. The preparation of country reports involved the creation of a guidance document to the country report; a webinar with national experts to discuss aim, context and methodology; interview with regulatory authorities; quality assurance to ensure comparative analysis of indicators, which were based on the objectives of the review of the legislation, such as incentives innovation and future proofing of the legislation.

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 (prepared by Utrecht University), MRI decentralized / mutual recognition procedures database, EudraGMP, and an EU shortages dataset collected from National

Competent Authorities for a bespoke European Commission study by Technopolis Group. The results of this are available in a separate Analytical report.

Case studies: seven areas were identified where a deeper analysis of a particular problem would be beneficial to support the impact assessment. These aimed at exploring the nature and evolution of the problem and link those to the proposed policy elements and their potential impacts. The analytical approach relied on document review, secondary data analysis and key stakeholder interviews. Selected case studies were: 1. Incentives for developing new antimicrobials. 2. Agile and adaptive regulatory systems. 3. Regulatory support for SMEs. 4. Improved access to medicines. 5. Generic competition and affordable medicines. 6. Regulatory barriers for emerging manufacturing technologies. 7. Criteria for unmet medical needs.

Stakeholder consultations: a number of different approaches were used in gathering evidence and views of stakeholders, which are summarized in a separate Synopsis report. These included a feedback to roadmap and a public consultation (both through the 'Have Your Say' EC website), a targeted survey, semi-structured interviews and two dedicated stakeholder workshops with civil society organisations, academic researchers, public authorities, healthcare professionals and industry.

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 (e.g. AMR), 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
- Any sensitivities or diverging views

This screening identified 10 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
- Resilience and technological sovereignty
- Public health & safety and health systems
- Sustainable consumption and production

3. Multi-criteria analysis

Evidence from all data sources was structured along each impact type for each policy element within policy blocks in each of the policy options. This exercise involved a triangulation of qualitative and where available quantitative data explored in the study. Where data gaps were evident, these were clearly noted and best judgement was used by study team members in the following scoring process.

A 7-point scale was adopted to quantify the scale of the impact and likely balance of costs or benefits with a grading system between -3 (significant negative impact expected for the specific impact type) through 0 (no impact is expected from applying a specific policy elements) to +3 (significant positive impact expected for the specific impact type), as compared with the baseline. In most cases, the directionality of impacts for stakeholders was gathered via stakeholder consultation and the extent of impact (performance) was assessed by the study team. Initial scores were given for policy elements in a policy block by study team members responsible for data triangulation for a specific policy block. Scoring across all policy blocks was then reviewed by a panel of three senior members of the study team to ensure consistency.

Multiple policy elements may act in concert or partially against one another when looking through the lens of specific impact types and so internal synergies and tension within a block were considered when overall scores were given. Note that weightings for all impact types were assumed to be 1. Synergies across policy blocks were more challenging to adequately quantify as in any multi-body problem the effects are not additive. Therefore, we provide a qualitative assessment of identified synergies and trade-offs in case specific policy options are simultaneously implemented in a policy option.

This approach allows for a rapid overview and ranking of policy options, for policy elements in a policy block, and suggest which scenario is expected to meet the specific policy objective with the significant positive impact.

4. Modelling changes in regulatory data and market protection system

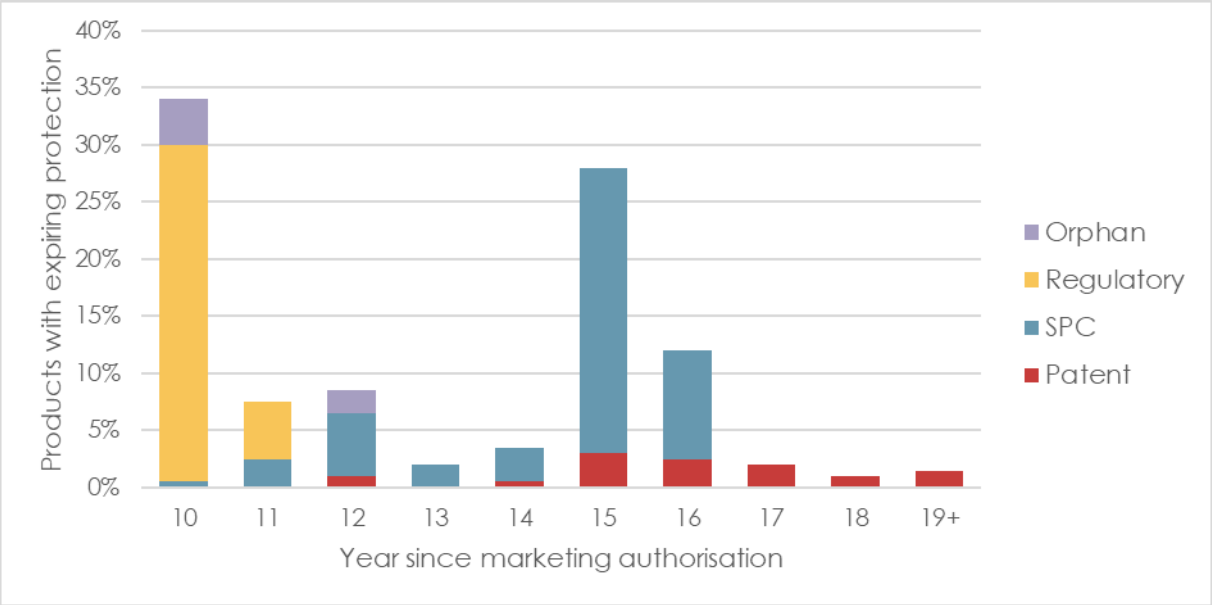
a. Protection types and length in a sample of medicines

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 in earlier years and other countries 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.

Of the 200 products that are on the market (not withdrawn), 69 products had currently regulatory data and market protection (RP) as last measure of protection. This means that 35% of the products in this sample would in principle experience reduced protection under a shortened standard regulatory protection system. Note however, that nine of these products had 24 months or less between RP and patent/SPC expiry and consequently, these products will be affected to a smaller extent by a two-year reduction of the standard RP period. We therefore estimate that 30% of all new medicines will be affected by a two-year reduction of the standard RP period.

The figure below shows that after 10 years from marketing authorisation date, 30% of products have RP expiry and 5% of products have RP expiry in year 11 (due to the additional year of regulatory protection for a new therapeutic indication of significant benefit). Close to half of the products have an SPC expiring as the last measure of protection, predominantly 15 years after marketing authorisation (the maximum value for the combined patent and SPC protection period from marketing authorisation), with a smaller fraction having additional paediatric SPC extension.

Figure 1 Distribution of protection expiry dates per type



Note however that while RP-protected products comprise about one third of the product basket, their share in total sales is only 23% of the total. The largest share of the total sales comes from SPC-protected product; when normalised per product, peak sales of SPC-protected products are 2.3 times higher than that of RP-protected products.

Table 1 Share and average peak sales of products under different protection types

Protection type	Share of total products	Average peak sales
Orphan	6%	€42m
Regulatory	34.5%	€158m
SPC	48%	€358m
Patent	11.5%	€257m

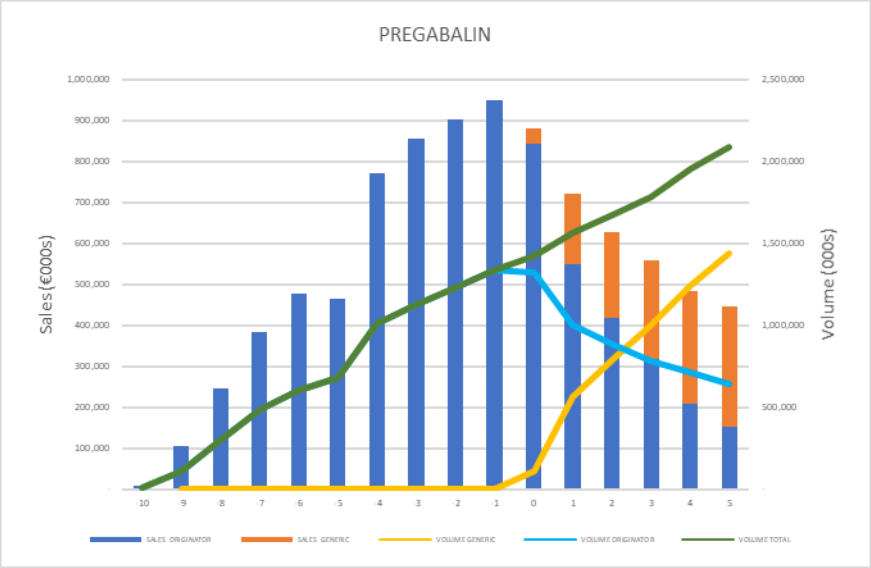
b. Developing an 'analogue' representing an innovative medicinal product lifecycle

We aim to generate an average sales revenue-volume graph that capture the lifecycle of innovative products over the protected RP period and that contested by generic/biosimilar medicines in the post RP expiry period. Since this requires a minimum of 16 years of consistent longitudinal data for a product, we used a cohort of medicines approved between 2004 and 2011, where RP is the last measure of protection. For practical reasons the cohort was split into two parts.

The first part included 20 products[9] (involving 2 biologic molecule) that have RP expiry dates between 2016-2021 and for these annual sales were calculated over a 10-year period pre-expiry. The second part included 16 products[10] (involving 1 biologic molecule) that have RP expiry dates between 2014-2016 and for these products annual sales were calculated over 5 years post expiry, along with annual sales data for their generic competitors. Note that 2 products were not contested after RP expiry but included in the cohort to allow for observing systemic effects. For example, the RP period for the biologic Cetuximab expired in 2014 and no biosimilar entered the market to date.

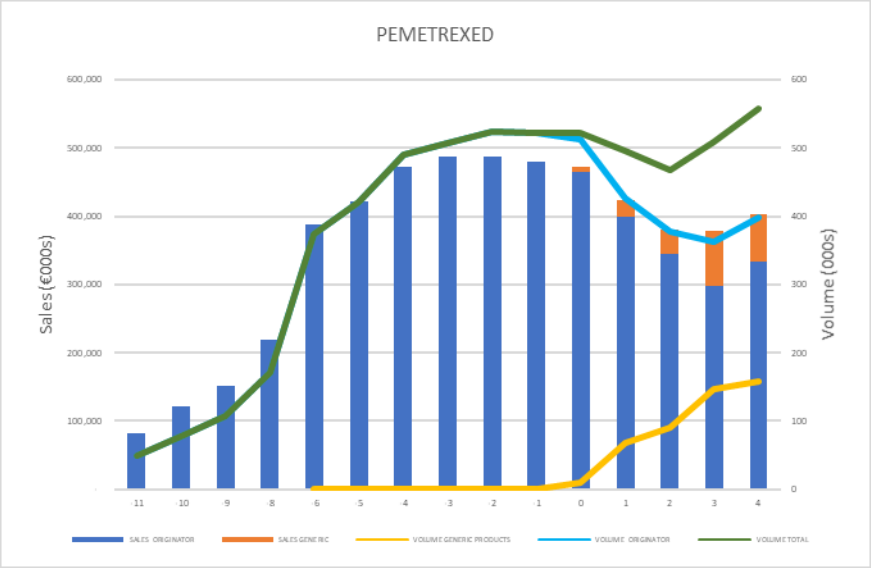
There is significant variation of the sales revenue-volume graphs across individual products, in some cases rapid generics entry erode the market value of the originator product, in other cases the originator maintains their market share, dependent on the level of sales generated by the originator. For two examples, please see the figure below:

Figure 2 Sales and volume data for two products from the 2014-16 cohort



[9] Products included: AGOMELATINE, AMLODIPINE!HYDROCHLOROTHIAZIDE!OLMESARTAN MEDOXOMIL, AMLODIPINE!HYDROCHLOROTHIAZIDE!VALSARTAN, AMLODIPINE!OLMESARTAN MEDOXOMIL, ANAGRELIDE, AZACITIDINE, CABAZITAXEL, CLEVIDIPINE, CLOFARABINE, DRONEDARONE, FEBUXOSTAT, GEFITINIB, *MIFAMURTIDE*, NELARABINE, PALIPERIDONE, PRASUGREL, ROFLUMILAST, SILODOSIN, ULIPRISTAL ACETATE, *VELAGLUCERASE ALFA*

[10] Products included: ALENDRONIC ACID!COLECALCIFEROL, ANAGRELIDE, CEFDITOREN PIVOXIL, *CETUXIMAB*, CLOFARABINE, DULOXETINE, EPLERENONE, FULVESTRANT, HYDROCHLOROTHIAZIDE!OLMESARTAN MEDOXOMIL, METFORMIN!PIOGLITAZONE, PEMETREXED, PREGABALIN, RASAGILINE, TIMOLOL!TRAVOPROST, TREPROSTINIL, ZONISAMIDE



We noted that very few biologics were found to be in the cohort for our analysis, however the biologics pipeline is growing (especially antibody modality, see Analytical report Table IEC1.3 and recent IQVIA report on biosimilar competition in Europe[11]) and expected to make a larger share of future product baskets. Biologics and biosimilars may have unique market dynamics because of differences in related development timeline and cost-profile. A comparative analysis of medicinal products launched between 1996-2014 shows that biologics are introduced faster and in more countries than non-biologic medicinal products[12] as it may be more profitable for developers compared to small-molecules. Switching from originator to biosimilars may also have different considerations, and recently launched biosimilars achieved over 50% uptake in their market within two years.[4] Examples of blockbusters (e.g. Humira, Herceptin and Enbrel) show that biologics are often protected by SPCs beyond RP expiry and biosimilars enter soon after expiry. In the RP cohort, we noted however another blockbuster example Xolair (Omalizumab) where RP as the last measure of protection expired in 2015 yet no biosimilar entry has taken place. While there is no current SPC on the product, there is a formulation patent until 2024 in force that may be constraining. In summary, it is not clear what share new biosimilars will have in future RP product cohorts where policy elements under considerations will be of effect. If the share of biologics substantially increases, it is likely that the general product sales/volumes model employed below will be less predictive.

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

[11] The Impact of Biosimilar Competition in Europe (2021) IQVIA. Available at: https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/iqvia-impact-on-biosimilar-competition.pdf

[12] Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe (2018) Copenhagen Economics. Available at: https://data.europa.eu/doi/10.2873/886648

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.

-

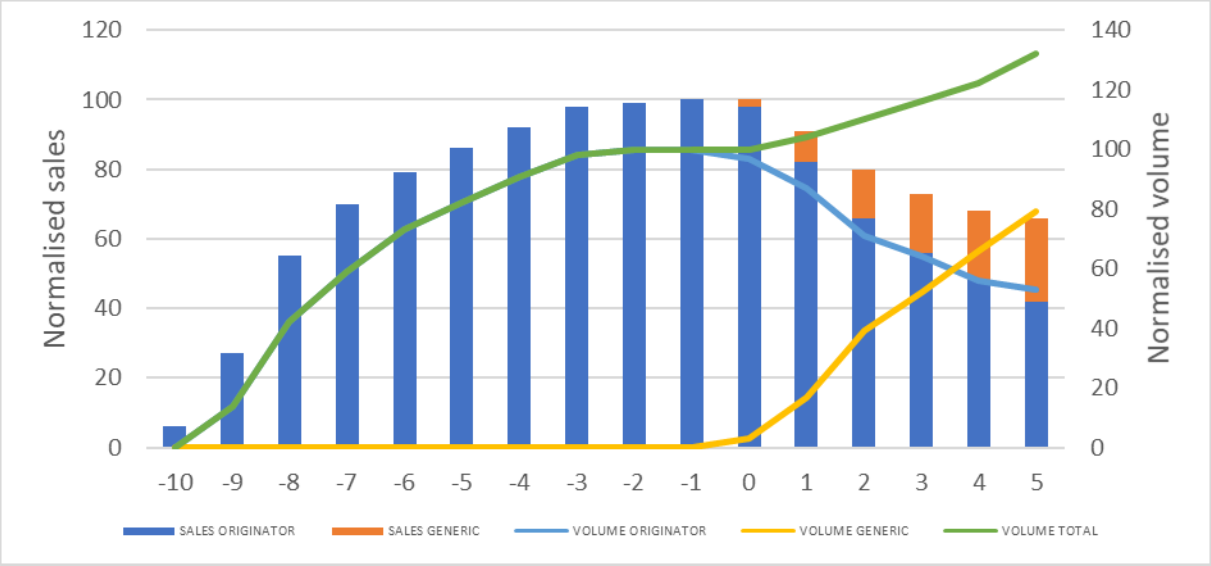
- **Generic sales**: generic industry operates on a high volume, low margin basis. With low product development risk, a lower profit margin can be sustainable. We apply a 33% gross profit margin on generic revenues.

The resulting table and corresponding figure are shown below:

Table 2 Normalised sales, volume, gross profit and price for products with RP 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 3 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.

The baseline is the current standard regulatory protection (for all medicinal products) of 8 years of data exclusivity plus extra 2 years of market protection, and in cases of additional indication with significant benefit +1 year of market protection.

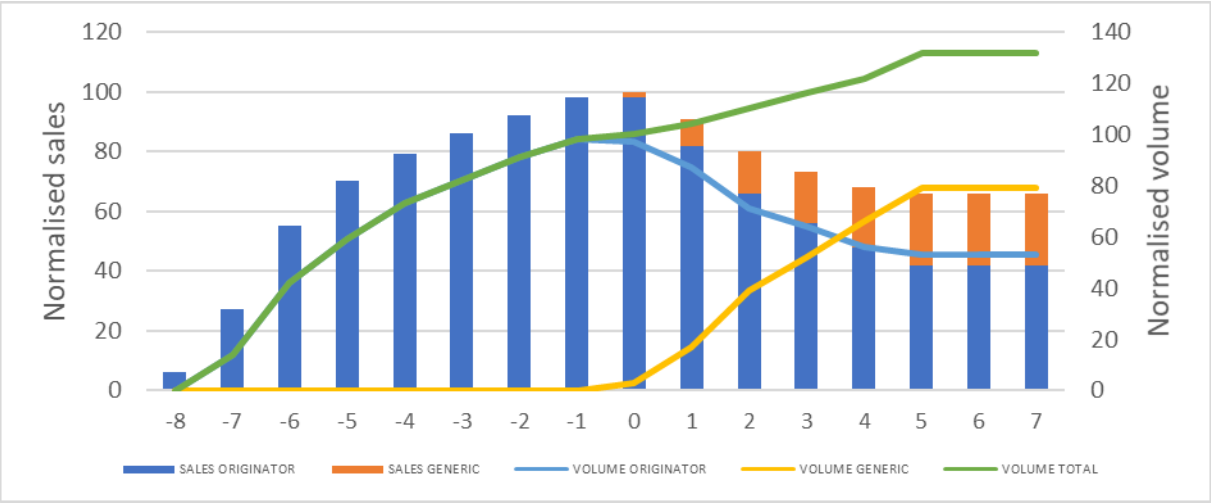
c. Modelling the economic impact of decreasing regulatory protection

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 RP loss over the product lifetime. It

should be noted again that this basket of products is dominated by small-molecule medicinal products; the lifecycle of biologics may be more extended given the absence of automatic substitution rules.

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 RP 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 RP regime will not change compared with the RP period of 8+2 years.

Figure 4 Normalised volume and sales data for products with 6+2 years of RP period



	Baseline	RDP 6+2	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 RP period is changed from 8+2 to 6+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[13] 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).

- 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. If we look at the annualised average price healthcare payers pay (calculated by dividing total sales and total volume in each year of the final 8 years of the product lifetime) in the different RP regimes, we note that, as expected, the average price drops faster to the equilibrium value in the case of the new standard RP regime (see Figure 5 below). If we consider the 'peak' volume sold of the originator product pre-expiry under the baseline situation and use the average price in each year under the different RP regimes to calculate post-expiry adjusted sales, we can assess the total savings healthcare payers would make in the RP 6+2 regime given equal volumes purchased. In the baseline RP 8+2 regime, the total lifetime sales is 1190 (normalised units) and in the new RP 6+2 regime the same volume at the new prices would be 1079 (normalised units). Thus in the RP 6+2 regime healthcare payers would pay -111 (normalised units) less, which is -9% less when considering the lifetime sales of the product.

[13] See https://www.drugdiscoverytrends.com/pharmas-top-20-rd-spenders-in-2021/

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 RP 6+2 regime it is 1123 (normalised units), equating to -67 (normalised units) or -6% saving to healthcare payers, on the products that are RP protected. Note, however, when considering the RP protected medicines represent some 20-23% 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 is marginal.

- Patients benefit due to the increased volume of the medicine sold after RP 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 standard RP 6+2 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 RP 8+2 regime. However, the extra volume of products available to patients manifest itself in the transition period between expiry and reaching the equilibrium value.

Figure 5 Normalised price of medicines over the final 8 years of the product lifetime

Monetising the systemic effects: Using the model in this study where only static effects are considered, we saw the normalised consequences for various stakeholders originating from a typical product where the last measure of protection to expire is RP. We can convert the normalised units to monetary value by equating the peak sales of 100 (normalised units) to the average peak sales calculated for the basket of RP products of approximately €160m per year. Note that per product level change should be considered as nominal since the actual individual product sales have a wide range around this average. At a systemic level, for a basket of products over years, however, the calculated values are expected to have predictive power.

Therefore, we need to assume the number of products per year to be affected by this policy measure. In the coming 15 years, we estimate that on average 40-50 new active substances will be authorised by EMA in each year (see Figure RI-9.1 and pipeline data in Analytical report and recent report[14]). From the current level of 30-40, we expect the baseline to evolve to 50-60 by the end of the period. As discussed, 30% of new authorised products are expected to be affected, however, products that address UMN or medicines with no return on investment (Option B) will not have reduced RP period. Overall, we estimate 20-25% of new medicines or 9-12 products will be affected annually by the measure.

[14] Global Trends in R&D, IQVIA Institute for Human Data Science, 2022. Available at: https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/global-trends-in-r-and-d-2022/iqvia-institute-global-trends-in-randd-to-2021.pdf

In the following we summarise the economic value calculated for each stakeholder group.

Table 1 Changes calculated between baseline and RP 6+2 per stakeholder group

Stakeholders	Product level change	% change	Annual systemic change (9-12 medicines)
Originator non-contested sales	**-€318m**	**-28%**	-€3,343m
Originator contested sales	**+€134m**	**21%**	+€1,411m
Originator gross profit	**-€188m**	**-15%**	-€1,969m
Generic sales	**+€77m**	**56%**	+€806m
Generic gross profit	**+€25m**	**56%**	+€266m
Cost to public payer	**-€107m**	**-6%**	-€1,126m
Patients treated	**+102**	**5%**	1,075
Δ of Patients treated (monetised)	**+€70m**	n/a	+€739
Patients + payer monetised gain/loss	**+€178m**	**+9%**	+€1,865

Note: colour code shows increased benefit/reduced cost (green) or decreased benefit/increased cost (red) to the stakeholder

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.

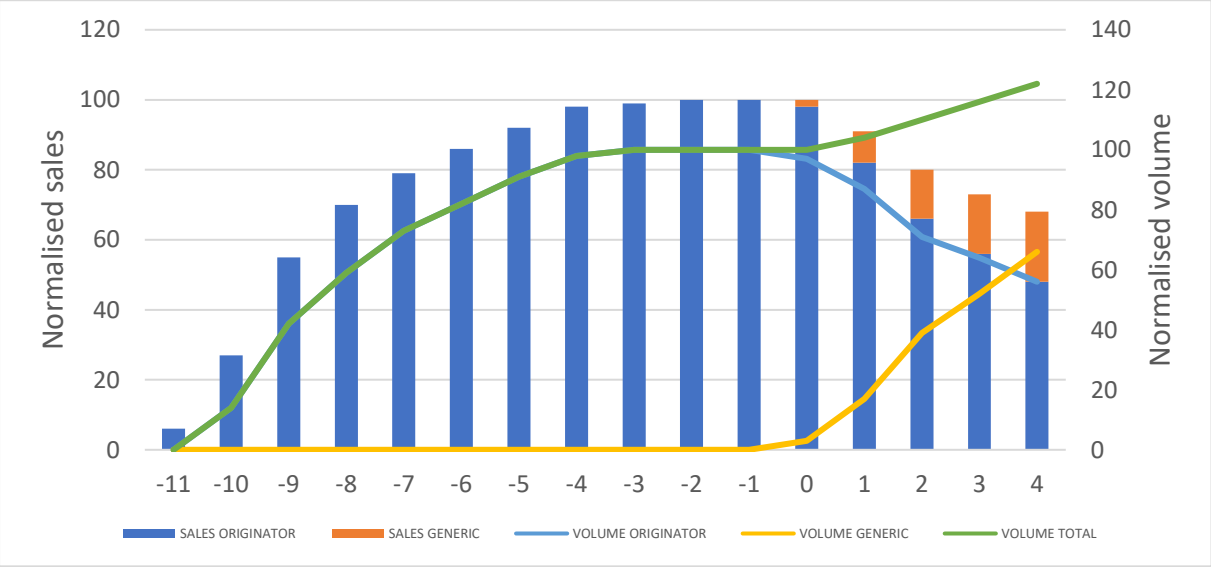
Business behaviour: There may be changes in the trajectory pre- or post-expiry compared to the current RP 8+2 regime, because companies change behaviour and aim to earn similar level of total pre-expiry monopoly rent during the reduced RP period. This may be achieved by

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 special incentives through increasing regulatory 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 RP period. We will use the result of this model to estimate the proportionate effect of incentives for 6 months (comparative trials, access incentive in option A) to 1 year (UMN incentive). Again, 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.

Figure 6 Normalised volume and sales data for products with 8+2+1 years of RP period



	Baseline	RDP 8+2 +1	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 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

Monetising the systemic effects for 1-year extension of RP for medicines addressing UMN (Option A and 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 40-50 annual new authorised medicines as per our dynamic baseline, 3 special UMN incentives per year is expected on average. It should be noted however that annual peak sales can deviate from the average value used in the model and for products with substantially larger expected annual revenue, the incentive may well worth the increased commercial cost/risk that is expected to be associated with developing a product that meet (at the early phases of development and up until authorisation) the UMN criteria.

Table 2 Changes calculated for 1-year extension of RP protection per stakeholder group

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
Δ of patients treated (monetised)	-€28m	-€84m
Patients + payer monetised gain/loss	**-€82m**	**-€246m**

Note: colour code shows increased benefit/reduced cost (green) or decreased benefit/increased cost (red) to the stakeholder

Monetising the systemic effects for 6-month extension of RP for comparative clinical trials (Option A and C)

Similar to the previous incentive, this measure could benefit RP-protected products, around 35% of all new medicines would be eligible. Conducting comparative trials should be feasible for many medicines, but not for all· Also, if the cost of the comparative trial is too high as opposed to the reward, companies will decide to decline the incentive. We expect that half of the RP products could benefit from it, or 8 medicines annually. Of course, higher sales medicines would have a higher compensation, regardless the cost of the trial.

It should be noted that this data is expected to generate new knowledge for better decision making at an earlier time point and thus represent additional fixed cost compared to baseline. We assume the additional costs of conducting comparative trial with standard of care amount to €20-50 m (the model uses the middle value of the range), referring to the paediatric trials as a benchmark[15]. Therefore the incentive could attract developers to factor in comparative trial design in their clinical study programme. There is no information on how stakeholders (including developers and regulators) would respond to statistically insignificant or negative outcome emerging from the comparative effectiveness arm of the study.

Table 3 Changes calculated for 6-month extension of RP protection per stakeholder group

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
Patients + payer monetised gain/loss	**-€41m**	**-€328m**

Note: colour code shows increased benefit/reduced cost (green) or decreased benefit/increased cost (red) to the stakeholder

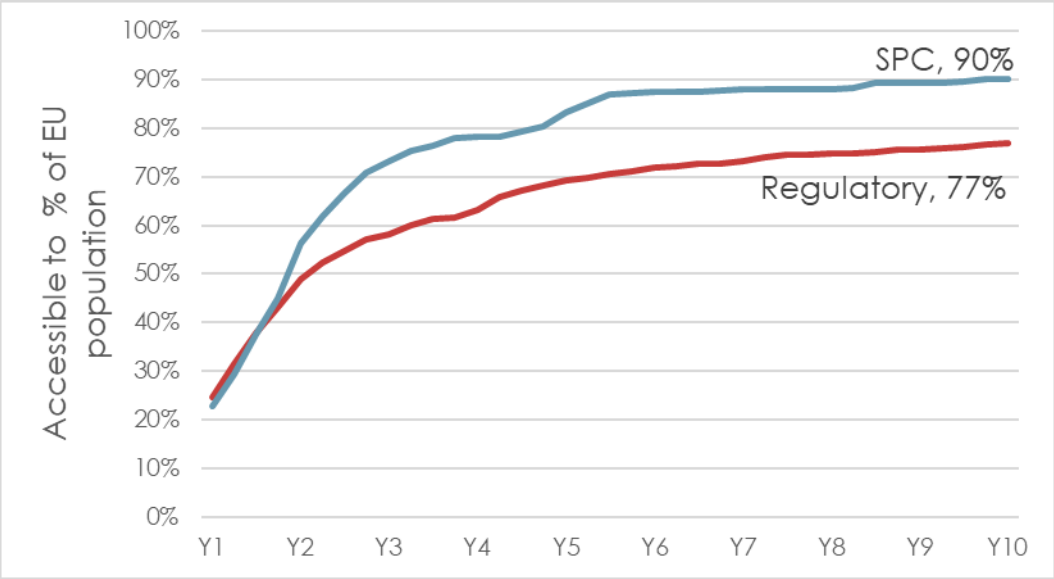
5. *Monetising the systemic effects of measures to improve market access*

The baseline is that there is no obligation or incentive to launch a product in a particular member state. Indeed, products authorised only reach up to 15 Member States (MS) out of the maximum possible 27 (Kyle, 2019) and on average 49% EMA-approved medicines are reimbursed in an EU country (Access case study; IQVIA, W.A.I.T. report 2021). Market launch incentives will not be a corrective measure for per capita utilisation rate of medicinal products but to increase the coverage across member states (breadth) and provide in some cases alternative medicinal products to existing therapies (depth) thereby creating positive spillover effects to better shortage management. Note that we had no access to IQVIA MIDAS sales data in three countries (Cyprus, Denmark and Malta) to ascertain market launch there.

[15] The joint evaluation of the orphan and paediatric regulation estimates the cost of paediatric studies at €22m.

We analysed products with protection expiry between 2016-2024 and recorded positive sales of originator products. For each molecule and each Member State, the first quarter in which meaningful non-zero sales occurred for at least two quarters. This is to eliminate cases where there may be one quarter of sales and then the product is not sold again in that Member State for several years. 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. We have also created a larger sample of products between Q1 2010 and Q4 2014. The patterns for the first seven years in the two samples were very similar. We analysed access as a function of the number of Member States in which each product was available and the corresponding percentage of the EU population that was covered for each product. Taking a simple average across all products gives a representative time series for all RP products and a separate representative time series for all patent/SPC products. This analysis shows that those products that are SPC-protected are accessible to a higher share of the EU population that those that are RP-protected.

Figure 3 Product accessible to EU population over time per protection type



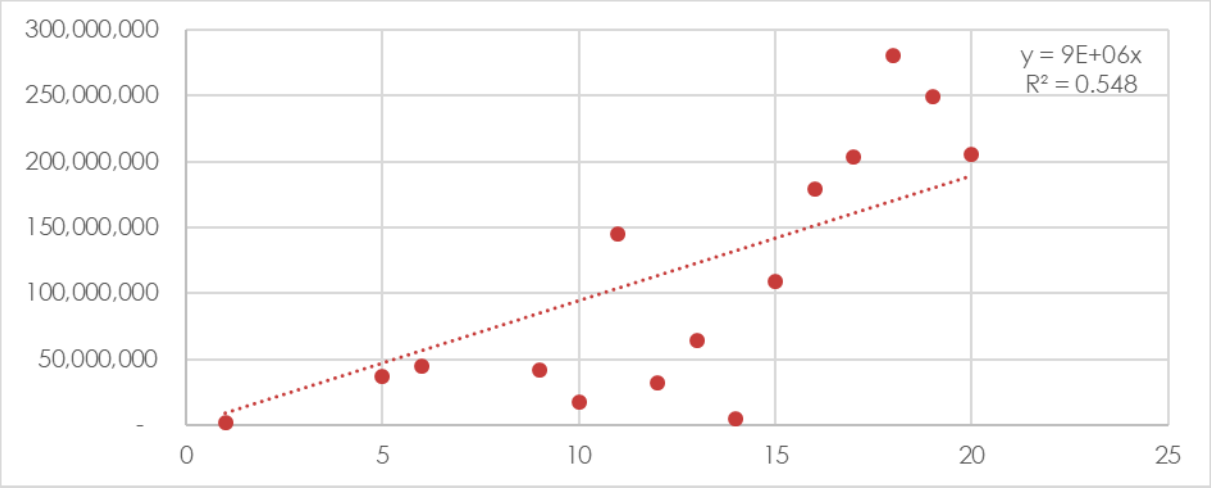
Deeper analysis point to higher coverage of products with higher sales and that larger member states with higher GDP tend to have a higher share of the products on their market. For example, there are 69 and 68 of the 78 products launched in Germany and Italy/Spain.

Table 4 Distribution of 78 products with RP expiry 2016-2024 launched in member states

Number of countries	Number of molecules	Percent	Cumulative %

where product was launched	launched		
1	3	3.9	3.9
2	1	1.3	5.1
3	2	2.6	7.7
4	2	2.6	10.3
5	2	2.6	12.8
6	3	3.9	16.7
7	1	1.3	18.0
9	2	2.6	20.5
10	2	2.6	23.1
11	5	6.4	29.5
12	3	3.9	33.3
13	6	7.7	41.0
14	2	2.6	43.6
15	5	6.4	50.0
16	5	6.4	56.4
17	5	6.4	62.8
18	7	9.0	71.8
19	12	15.4	87.2
20	10	12.8	100.0

Figure 4 Average annual peak sales of products with RP expiry 2016-2024 per country launch



The different options use different policy measures to enhance access to patients. Option A provides an additional RP period of +6 months in case centrally authorised product is placed on all EU market within 5 years of MA. Option B involves obligation to place a centrally authorised medicine on the market in the majority of MS. Finally, option C provides a milestone incentive of +2 year of RP period if a medicinal product is supplied in all MS within a period of 2 years from MA.

Based on the size of the incentives/losses we estimated the compliance as percentage of medicines. From this, we could calculate the costs or savings to the public (Table 5). 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, we used a higher average peak sales in the model, €255m, the average of the higher-selling half in our basket of RP protected products. For option B and C, the model of the reduced regulatory protection was used (from option B), to calculate public savings stemming from non-complying medicines. Again, we adjusted the average peak-sales value (to €80m), assuming that the low-sales medicines will be the ones not complying.

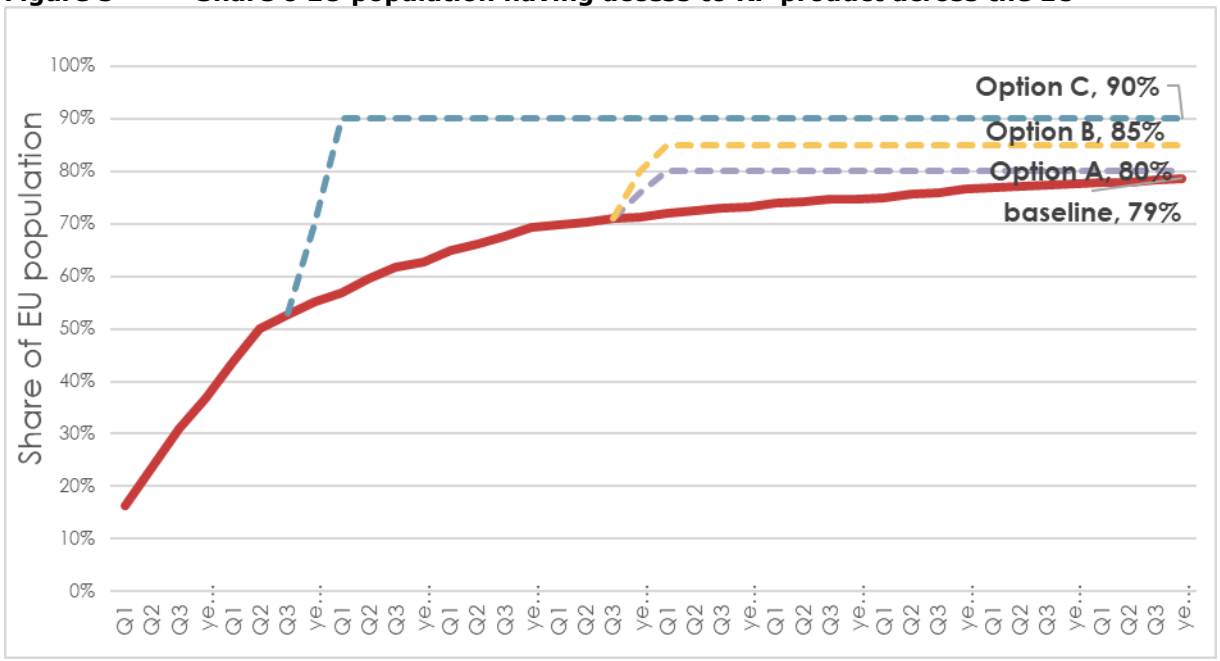
Table 5 Compliance estimate for each option, commercial value and cost/benefit for public

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	66% (10-12 medicines)	-€469 m gross profit	€444 m gain from non-

-2 years, if not in all EU		-15% gross profit for 5 non-complying medicines	complying medicines

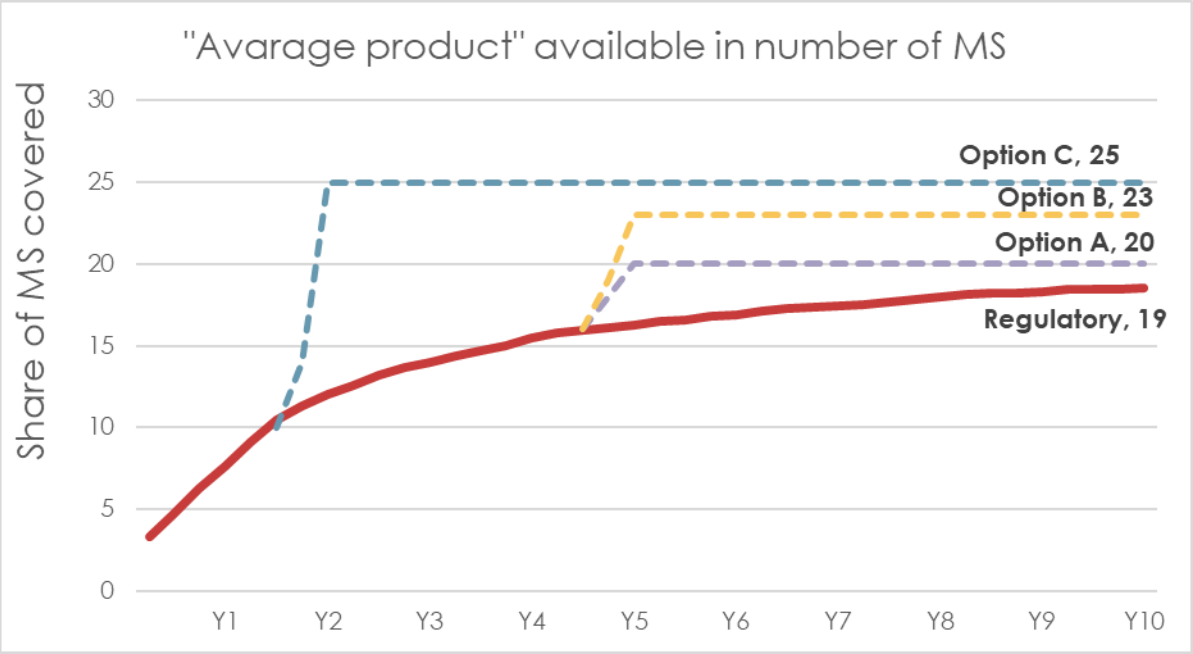
Again, launching products in all EU member states requires additional investments by companies compared to baseline, which will reduce the net gain experienced by companies.

Figure 5 Share o EU population having access to RP product across the EU



Option	Average coverage over 10 years % population	Average coverage over 10 years Number of member states
Baseline	65.3%	15
Option A	67.6%	16
Option B	70.2%	18
Option C	80.1%	23

Figure 6 Social impact of enhanced access to RP product across the EU



6. AMR transferable voucher

Antimicrobial resistance is a global challenge and the cost of inaction is very high when compared to expected societal benefits and cost savings in the mid/long term[16]. Antimicrobial products are not expected to be sold in large volumes on the market or generate large revenue stream and therefore the commercial incentive through the RP system will have limited value. Developers of antimicrobials are often innovative SMEs without significant resources to take these products through the regulatory approval pathway and require alternative instruments for ensuring sustainable R&D of antimicrobials. A transferable regulatory protection voucher (or transferable exclusivity voucher) allows the developer of an antimicrobial product to benefit from an additional year of data exclusivity period on another product in their portfolio or sell the voucher to another company that would use the voucher for their own benefit. This mechanism could provide the developer a reward (or an incentive) for

[16] https://www.oecd.org/health/health-systems/Averting-the-AMR-crisis-Policy-Brief-32-March-2019.PDF

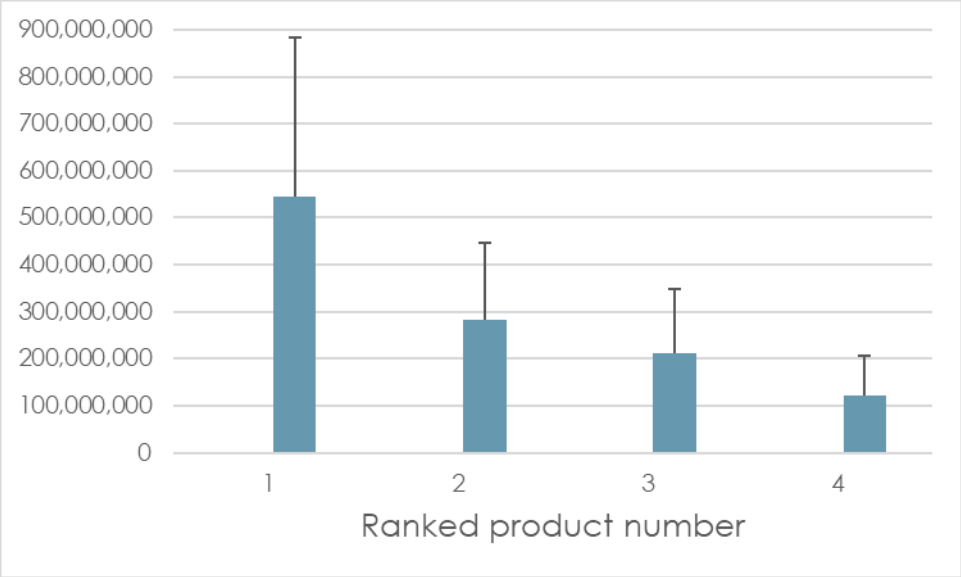
developing an antimicrobial product and meet (partially) the related investment needs of an estimated €1bn per product. [17] While the reward will directly be paid to developer by the buyer of the voucher, the cost of the voucher would eventually be met by healthcare payers of the product developed for other diseases (potentially also benefitting from lower level of AMR).

The transferable voucher is therefore only applicable to a subset of products where RP is the last measure of protection rather than those with patent/SPC. As we noted above, products with high peak sales tend to have SPC as LOP, and thus on average, the cohort of products with RP as LOP will have lower peak sales.

It should however be pointed out that when the voucher is sold on, only part of the value will be captured by the developer of the antimicrobial product (the seller) and the other part will go to the buyer of the voucher. The larger the share that goes to the seller, the more efficient the voucher is as an incentive or reward to develop antimicrobial products.

It has been observed, in the case of the priority review voucher introduced in the USA, that the more vouchers are available for the buyer, the lower price the buyer needs to pay and hence a larger share of the value is retained by the buyer.

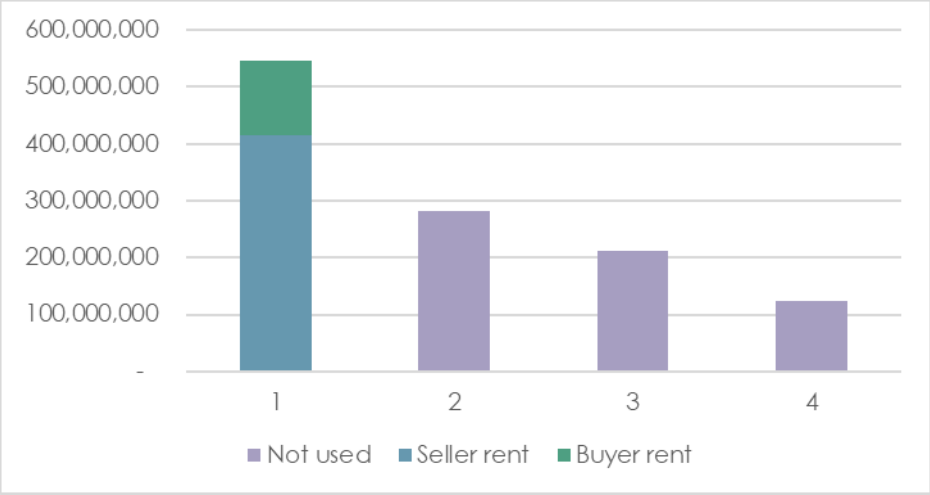
Figure 7 Average peak annual sales of products with RP expiry 2014-2024



[17] New drugs to tackle antimicrobial resistance (2011) The Office of Health Economics

The ‘erosion’ of the value of the voucher will increase with increasingly more vouchers concurrently available on the market. Similarly, the seller’s share is changing dependent on the number of vouchers simultaneously competing for products to transfer the voucher to. In the figures below, we see that share that goes to the seller of the voucher (i.e. developer) will decrease and the total incentive in the system reach a plateau. Thus the system designed to support the developer becomes less efficient. Note that the total incentive plateau is at about €500m that is half of the expected development cost of an antimicrobial product. It is therefore clear that the transferable voucher in this model will not cover the total development cost of the developer.

Figure 8 Share of the seller and buyer in the value of the voucher for (top) n=1 voucher per year and (bottom) n=3 vouchers per year



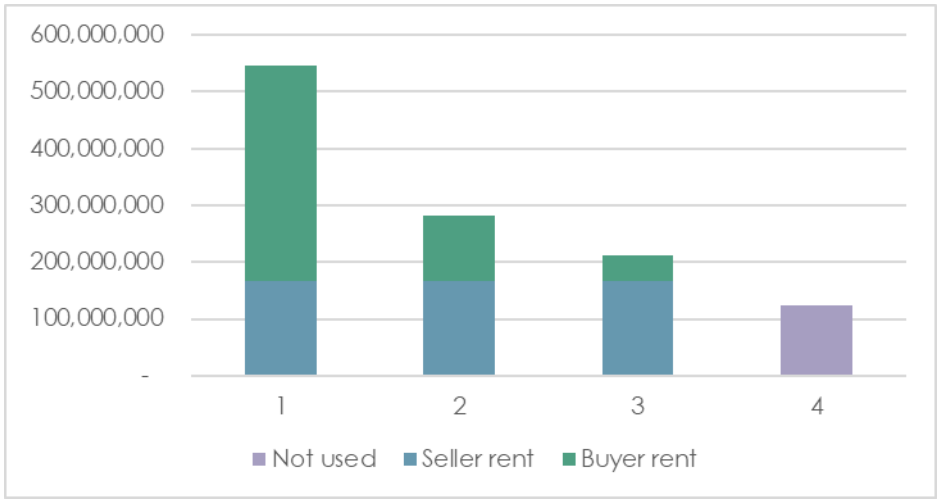
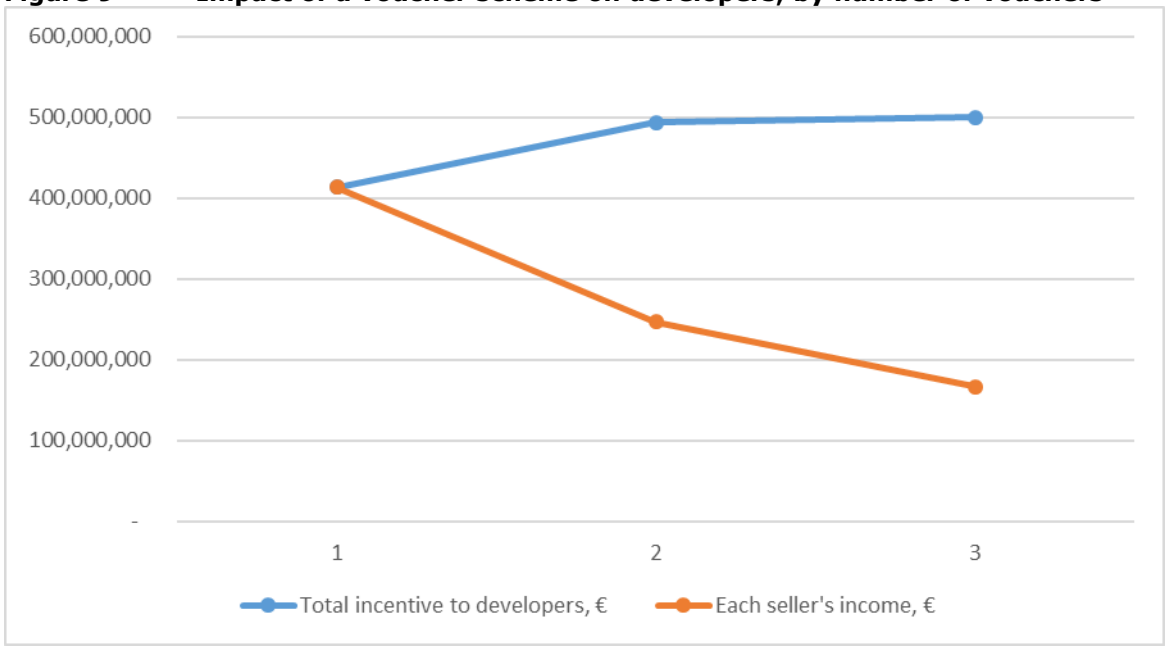
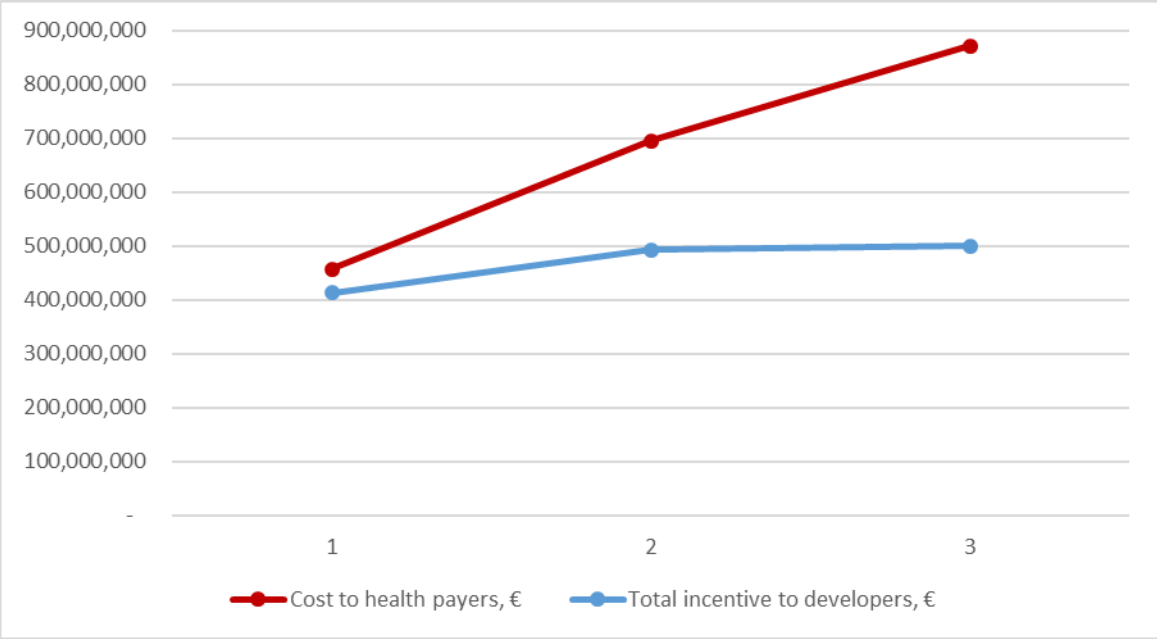


Figure 9 Impact of a voucher scheme on developers, by number of vouchers



The cost to healthcare payers (i.e. difference of peak sales and equilibrium sales for a given product) will also increase from a value initially close to the value of the voucher (1.1 times the total incentive) to a higher multiple of 1.75. Note however this analysis compares only the cost rather than the benefit of developing antimicrobials. OECD estimates that AMR already costs about €1.1bn every year to the EU Member States healthcare systems.

Figure 10 Comparison of total incentive to developers and total cost to health payers, by number of vouchers



The distribution of the average peak sales of products that have RP expiry as LOP and the number of vouchers will therefore determine the cost and benefit to the various stakeholders. In our cohort we focussed on high-revenue products and therefore we used a normalised product sales and volumes curve that is expected to represent this cohort of products more closely (i.e. higher rate of generic entry and originator price erosion, see Figure 2). We use the model introduced earlier and apply to the three scenarios that link to the number of simultaneous vouchers in issue. The corresponding costs and benefits are detailed below:

1. Three transferable vouchers are granted per year

For originators: The top three products in each year will benefit from an extra year of RP extension; using the average values for these (€545m, €283m, and €211m) we obtain €872m per year net gain in revenue compared to baseline, which accumulates to €13.1bn over 15 years for

originators at current euro values. The corresponding share of innovation budget generated for industry (20%) is €174m annually or €2.6bn over the 15 years.

For developers: The figures earned by originators may be compared to the amount they had paid as buyers of the transferable vouchers to antimicrobial developers as sellers of the vouchers. Developers obtain €500m for their three vouchers annually or €7.5bn over the 15 years. While no discount is considered for cost of goods and cost of capital for originators, these companies can afford the cost of the voucher as the annual net gain from the extended RP is greater than the annual cost of the vouchers. Nevertheless, it is worth noting that the annual €174m innovation budget generated through the RP extension does not cover the cost of buying the transferable vouchers from sellers. Finally, the total AMR development incentive of €500m shared across three developers provides a fraction of the development cost of three antimicrobial products (about 17%) they had invested in.

For generic companies: The cost of delayed market entry for generics of the three products per year was calculated as €322m or €4.8bn over 15 years.

For healthcare payers: The nominal cost calculated at constant peak volume of the originator product sold, national healthcare systems pay an additional €561m compared to baseline per year or €8.4bn over 15 years.

For patients: Patients have costs and benefits associated with the voucher: Developing antimicrobials has a significant patient benefit that is hard to monetise but as pointed out before, any reduction of the current high cost of AMR (€1.1bn per year) in the national healthcare systems is the ultimate aim of the voucher system. As before, we may attribute the share of the revenue for innovation (€174m per year, or €2.6bn over 15 years) or better the amount originators pay developers for the vouchers (€500m per year that is €7.5bn over 15 years) as patient benefit.

However, patient will not be served from lower coverage of the other products that are protected by an extended RP period compared to baseline, with reduced volume distributed to patients -55 (normalised units) or a reduction of -4%.

2. One transferable voucher is granted per year

For originators: Only the top selling product in each year will benefit from an extra year of RP extension; using the average value for this (€545m) we obtain €458m per year net gain in revenue compared to baseline, which accumulates to €6.9bn over 15 years for originators at current euro values. The corresponding share of innovation budget generated for industry (20%) is €92m annually or €1.4bn over the 15 years.

For developers: The developer that obtained the voucher will obtain €413m (as the average price of the top and top+1 product) in each year or €6.2bn over the 15 years. It appears that the annual net gain from the extended RP companies earn is sufficient to pay the price of the voucher. The AMR development incentive of €413m for one developer in each year provides a larger fraction of the development cost of an antimicrobial product than the previous scenario where three developers shared the total incentive.

For generic companies: The cost of delayed market entry for generics of the product with extended protection was calculated as €169m per year or €2.5bn over 15 years.

For healthcare payers: The nominal cost calculated at constant peak volume of the originator product sold, national healthcare systems pay an additional €294m compared to baseline per year or €4.4bn over 15 years.

For patients: Again, we can attribute the share of the revenue for innovation (€92m per year; €1.4bn over 15 years) or better the amount originators pay developers for the vouchers (€413m per year; €6.2bn over 15 years) as patient benefit.

However, patient will lose coverage of the product that is protected by an extended RP period compared to baseline, which through a reduced volume distributed to patients can be equated to €305m per year or €4.6bn over 15 years.

3. Transferable voucher is granted every two years

Here we assume that only the top selling product will benefit from an extra year of RP extension every other year. There is however the potential for higher selling products on the market. The Table below It does not appear to provide any further efficiency gain in the system compared to the previous scenario and selecting this makes no policy sense as a large share of the originator's gain will already have been paid to developers, long before originators can reap the benefits of their investment. Of course, if there is no qualifying antimicrobial for a transferable voucher each year (which may well be the case if no sufficient incentive/profit margin exist in the system) pipelines will dry up, and the system will have reduced direct costs and benefits for all stakeholders. Nevertheless, there remains a distinct risk that a resulting lack of preparedness for a future pandemic of antimicrobial resistance will be counted in trillions of euros lost globally.

Table 6 Average peak annual sales of top products with RP expiry 2014-2024 segmented bi-annually

Year (RP expiry)	Top 1 (sales, €)	Top 2 (sales, €)
2014-2015	978,000,000	493,000,000
2016-2017	473,000,000	120,000,000
2018-2019	469,000,000	386,000,000
2020-2021	703,000,000	408,000,000
2022-2023	1,270,000,000	174,000,000
AVERAGE	**778,600,000**	**316,200,000**

STD	345,033,766	160,680,428

7. Costs and benefits of Option C (preferred option)

Table 7 summarises the benefits and costs for the preferred option by adding up the different elements from the previous sections.

Table 7: costs and benefits of pivotal measures in the preferred option

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 new antibiotic	+€387m gross profit (1 voucher)	- €54m gross profit
Total balance	**+ €571m cost** + 1-2 new UMN medicines +comparative clinical data +15% access +1 new antibiotic	**+€298m gross profit**	**- €82m gross profit**

Table 8 summarises costs and benefits of the horizontal measures.

Table 8.: costs and benefits of horizontal measures in the preferred option

		1 year average	**15 years average**			**1 year average**	**15 years average**
Benefits (horizontal measures)				**Costs (horizontal measures)**			
Streamlining savings for businesses	€ millions	22	337	Streamlining costs for regulators	one-off	25.2	25.2

Streamlining savings for regulators	€ millions	50	754	Streamlining costs for regulators	recurrent	50.5	757.5
Streamlining income for generics	€ millions	82	1,237	**Sum of costs (streamlining)**	**€ millions**	**75.7**	**782.7**
Sum of benefits (streamlining)	**€ millions**	**155**	**2,329**	Digitalisation costs for regulators	one-off	235	235
Digitalisation savings for businesses	€ millions	11	169	Digitalisation costs for regulators	recurrent	47	705
Digitalisation savings for regulators	€ millions	100	1,507	**Sum of costs (digitalisation)**	**€ millions**	**282**	**940**
Sum of benefits (digitalisation)	**€ millions**	**112**	**1,676**	Enhanced support for SMEs and non-commercials	cost for industry (recurrent)	2	30
Enhanced support for SMEs and non-commercials	€ millions	11	169	Enhanced support for SMEs and non-commercials	cost for regulators (recurrent)	6	90
		7	112	**Sum of costs (SME support)**	**€ millions**	8	120
		3	39	**TOTAL costs**	**€ millions**	**2,169**	**28,891**
Sum of benefits (SME support)		**21**	**321**				

TOTAL benefits	**2,273**	**34,101**					

The preferred option has a variant too, in which the RP is 6+2, but by launching in all Member States the incentive is only 1 year additional protection. Table 9 summarises the costs and benefits in that case:

Table 9. 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 new antibiotic	+€387m gross profit (1 voucher)	- €54m gross profit
Total balance	**+ €377m gain** + 1-2 new UMN medicines +comparative clinical data +8% access +1 new antibiotic	**-€602m gross profit**	**+€39m gross profit**

Methodology and analytical models used for the evaluation

This section summarises the methods used for task 2 (data identification, collection and analysis) and task 3 (stakeholder consultations). The tables below outline the specific work packages and the related outcomes of how the findings were used and/or reported.

Table 10. Task 2: Data identification, collection and analysis.

Work package	Outcomes and reports
2.1 Literature Review	Integrated throughout analytical report, case studies,

	evaluation report and impact assessment.
2.2 Comparative Legal Analysis	7 Country reports
2.3 Secondary Data Analysis	Analytical Report
2.4 Case Studies	Case Study Report and Case Studies

Table 11**.** Task 3: Stakeholder consultations.

Work package	Outcomes and reports
2.1 Literature Review	Integrated throughout analytical report, case studies, evaluation report and impact assessment.
2.2 Comparative Legal Analysis	7 Country reports
2.3 Secondary Data Analysis	Analytical Report
2.4 Case Studies	Case Study Report and Case Studies
3.2 Feedback Analysis	5-page report annexed to the inception report
3.3 Public Consultation	Integrated throughout analytical report, case studies, evaluation report and impact assessment.
3.4 Targeted Survey	Annex to the evaluation report
3.5 Interviews	Individual interview summary notes and integrated throughout analytical report, case studies, evaluation report and impact assessment.
3.6 Workshops	Workshop summary notes (2)

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 (e.g. EFPIA, EuropaBio, Medicines for Europe) 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 12) 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 13). In some cases, interviewee's opted to provide written feedback which was accepted and annexed to the report.

Table 12**.** Interview Schedule.

Country	Contacted and 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 13**.** 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[18] 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 14 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 14**.** 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

[18] Specific Measurable Achievable Relevant Timebound

	(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 15. 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 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 15. 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.

Alongside ongoing data identification, collection and analysis the 'focus areas' of each case study were agreed iteratively with the EC. 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. Seven case study topics were agreed: 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 next 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 (0.5 pages)
- Retrospective view
    - 1: Nature and extent of the problem (1 page)
    - 2: Objectives of the 2004 regulation (0.5 page)
    - 3: Evaluation of the achievements of the regulation (2 pages)
- Forward looking view
    - 1: Evolution of the problem and residual challenges (1 page)
    - 2: Enhanced policy options (2 pages)
    - 3: Potential impacts of the revisions (2 pages)
    - 4: Synergies and interplay (1 page)

- 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 16) 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 16. 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): 1 resources (capital, human, etc.) 2 risks 3 collaborations (relationship w/large companies, knowledge institutes) 4 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			

Further information including search terms and inclusion and exclusion criteria for each case study specifically plus the seven case studies can be found in the Case Study Report.

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 17) 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 17. OPC survey structure.

1) Backward-looking questions • Other issues to be addressed in this revision • Positive and unintended effects of the legislation **2)** 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 500 responses would be received and in total 478 responses were received – shown below -by stakeholder group.

Table 18. 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 19 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 19. 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 20.

Table 20. 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 21 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 21. 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 22.

Table 22. 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

ANNEX 5: EVALUATION

The Evaluation is provided in a separate document, in attachment.

ANNEX 6: COHERENCE WITH THE REVISION OF THE ORPHAN AND PAEDIATRIC REGULATION

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).

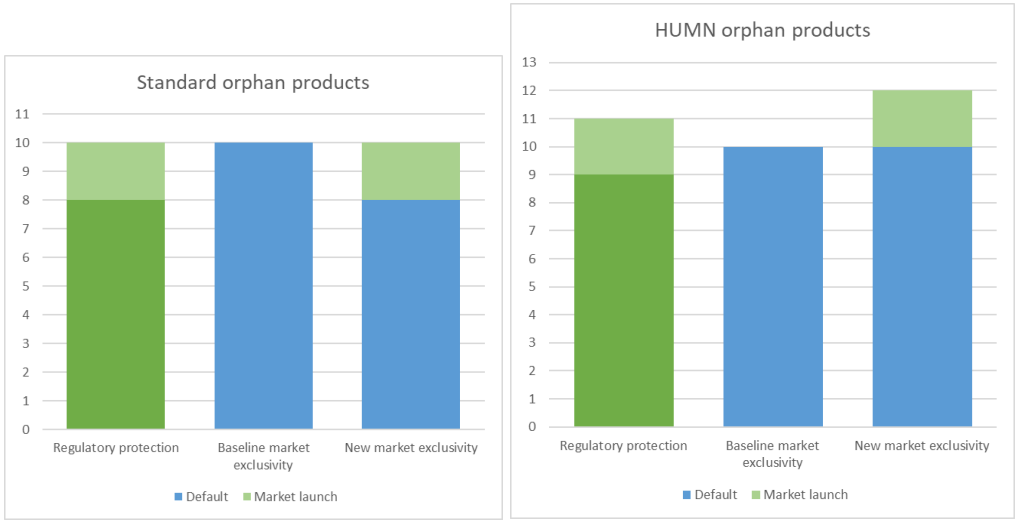
In principle, medicines that satisfy the definition of UMN or HUMN will receive (a) access to early scientific advice and regulatory facilities and (b) access to longer regulatory protection periods (market exclusivity for medicines for rare diseases and data protection for other medicines).

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 below graph demonstrates the interplay among the two protections for orphan medicines, with the 2-year market launch conditionality:



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.

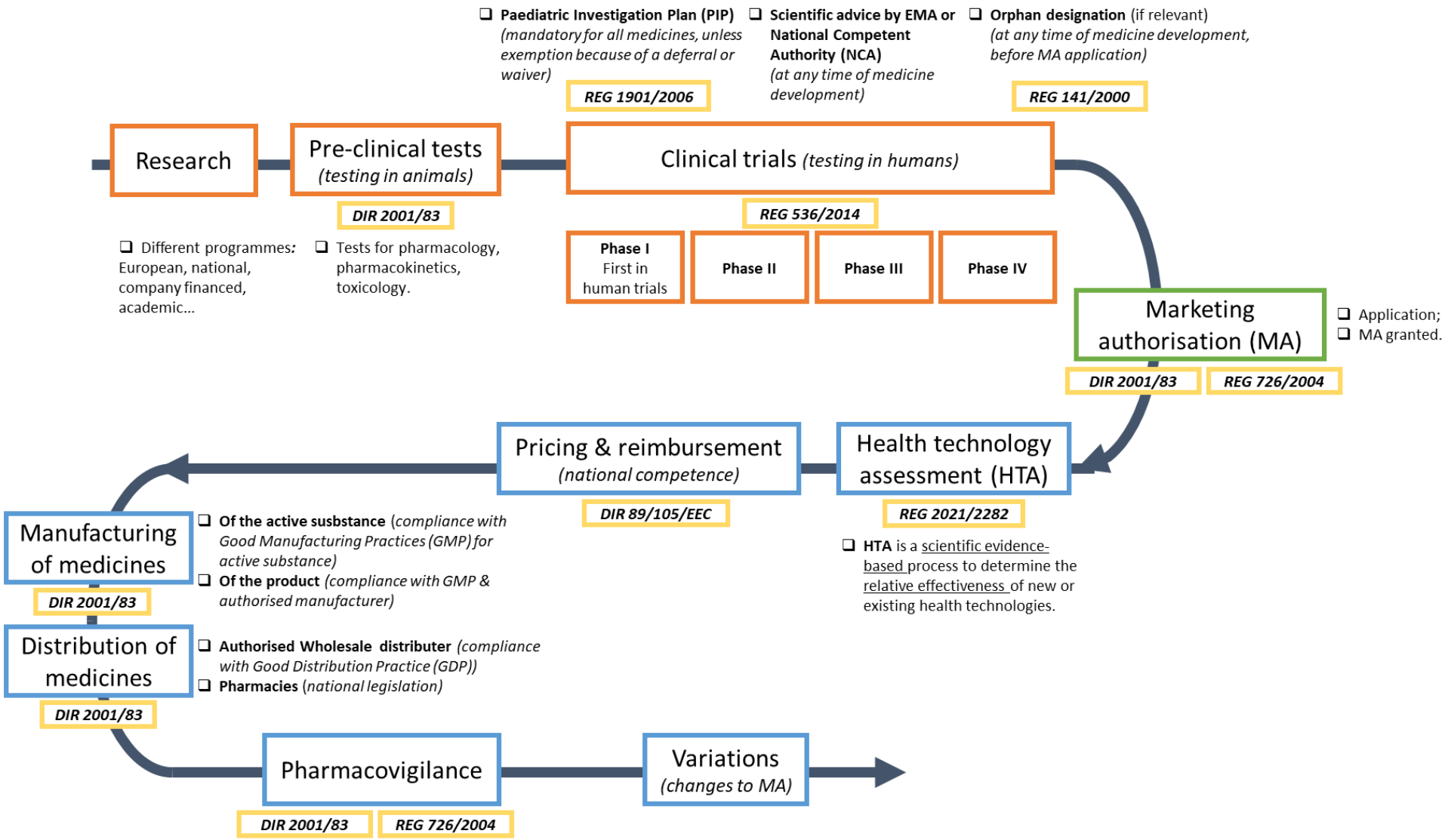
In the case of transferable exclusivity vouchers (TEVs), at first glance, there may seem to be incoherence between the two regimes. The conclusion in the Impact Assessment for the revision of the legislation on medicines for rare diseases is that TEVs can be considered as an ineffective incentive to 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.

ANNEX 7: OVERVIEW OF MARKETING AUTHORISATION PROCEDURES

ANNEX 8: VISUAL OVERVIEW OF THE LEGAL FRAMEWORK

National procedure	Mutual recognition procedure (MRP)	Decentralised procedure (DCP)*	Centralised Procedure (CP)
… where one MS authorise medicines for its own territory.	**…where additional MSs recognise the national MA of another MS and authorise the medicine for their own territory.**	**…where several MSs authorise a medicine for their own territory.**	**…where a MA is valid in all MSs.** **This procedure is <u>mandatory</u> for some products.**
Market access			
National territory.	**National territory of all MSs involved.**		**EU internal market.**
Procedure overview			
Procedures and assessment time depend on national legislation.	**Based on MA already granted by one MS;** **Recognition of that MA by other MSs.**	**Scientific assessment by one MS;** **Consultation of MSs involved.**	**Scientific assessment by EMA;** **Consultation of the MSs;** **Authorisation granted by COM.**
	Total time if agreement among MSs ***→ 210 days***	***→ 240 days***	**Total time if positive opinion by EMA** ***→ 277 days***
	If disagreement among MSs → referral procedure to CMD(h)/ CHMP		


❑ Paediatric Investigation Plan (PIP) (mandatory for all medicines, unless exemption because of a deferral or waiver)
REG 1901/2006
❑ Scientific advice by EMA or National Competent Authority (NCA) (at any time of medicine development)
❑ Orphan designation (if relevant) (at any time of medicine development, before MA application)
REG 141/2000
Research
Pre-clinical tests (testing in animals)
DIR 2001/83
Clinical trials (testing in humans)
REG 536/2014
❑ Different programmes: European, national, company financed, academic…
❑ Tests for pharmacology, pharmacokinetics, toxicology.
Phase I First in human trials
Phase II
Phase III
Phase IV
Marketing authorisation (MA)
DIR 2001/83
REG 726/2004
❑ Application;
❑ MA granted.
Health technology assessment (HTA)
REG 2021/2282
❑ HTA is a scientific evidence-based process to determine the relative effectiveness of new or existing health technologies.
Pricing & reimbursement (national competence)
DIR 89/105/EEC
Manufacturing of medicines
DIR 2001/83
❑ Of the active susbstance (compliance with Good Manufacturing Practices (GMP) for active substance)
❑ Of the product (compliance with GMP & authorised manufacturer)
Distribution of medicines
DIR 2001/83
❑ Authorised Wholesale distributer (compliance with Good Distribution Practice (GDP))
❑ Pharmacies (national legislation)
Pharmacovigilance
DIR 2001/83
REG 726/2004
Variations (changes to MA)

ANNEX 9: OVERVIEW OF ECOSYSTEM AND THE LEGAL FRAMEWORK

1. The pharmaceutical ecosystem

The Pharmaceutical Strategy for Europe[19] 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[20].

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[21]. Overall, it covers **24.8 million direct jobs**, **493 000 firms** (including 99.7% SMEs) and contributes to **9.5% of EU value added**[22]. 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%[23]. 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[24].

In the ecosystem, 'big pharma'[25] are increasingly outsourcing functions, including clinical trials and manufacturing, and are focusing investment on a limited number of therapeutic areas while disinvesting from others[26]. Emerging biopharma companies – often SMEs – are driving a large portion of innovation and development. According to a recent report from IQVIA[27], 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.[28]

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 companies or start-ups with promising portfolios of patents[29]. 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

[19] COM(2020) 761 final.
[20] COM(2021) 350 final European industrial strategy | European Commission (europa.eu).
[21] SWD(2021)351 final – page 138.
[22] SWD(2021)351 final – page 137.
[23] Would the last pharmaceutical investor in Europe please turn the lights out (efpia.eu).
[24] SWD(2021)351 final – page 139.
[25] Understood as multinational companies dominating the industry sales and traditionally responsible for all aspects of the medicines discovery pipeline.
[26] European pharmaceutical research and development. STUDY Panel for the Future of Science and Technology. European Parliament Research Service, p. 10.
[27] Global Trends in R&D: Overview through 2021, IQVIA, February 2022.
[28] Ibid, footnote 27.
[29] Ibid, footnote 27.

pharmaceutical sector, though small firms and start-ups also rely on venture capital to finance their R&D.[30]

2. The 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. harmonises the way medicines are authorised across the EU. This legislation is 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.

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.

The general pharmaceutical legislation also regulates the post-authorisation monitoring of the medicine (pharmacovigilance), as well as manufacturing, distribution and advertising.

The **specialised legislations for rare diseases and children**[31] ("The Orphan and Paediatric Regulations") complements 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 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[32]. Taken together, they aim to ensure the right balance between giving incentives for innovation to

[30] Kyle M., 'The Alignment of Innovation Policy and Social Welfare Evidence from Pharmaceuticals', Innovation Policy and Economy 20, 2020.

[31] Regulation (EC) No 141/2000 of the European Parliament and of the Council on orphan medicinal products, OJ L 18, 22.1.2000, p. 1, EUR-Lex - 32000R0141 - EN - EUR-Lex (europa.eu) and Regulation (EC) No 1901/2006 of the European Parliament and of the Council on medicinal products for paediatric use, *OJ L 378*, 27.12.2006, p. 1, EUR-Lex - 32006R1901 - EN - EUR-Lex (europa.eu).

[32] However, the revision of the general pharmaceutical legislation has also other aims (such as ensuring that medicines are affordable, reducing environmental impact), not covered by the revision of the specialised legislations.

strengthen the research base of the EU pharmaceutical industry and the need for patients to have access to affordable medicines.

Advanced therapy medicines[33] 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**[34] 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.

The **proposed Regulation on the European Health Data Space** (EHDS)[35] 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)[36] 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**[37] (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

[33] 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.

[34] 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 https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32014R0536&qid=1653648430017.

[35] 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).

[36] For more details, see https://eic.ec.europa.eu.

[37] 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)

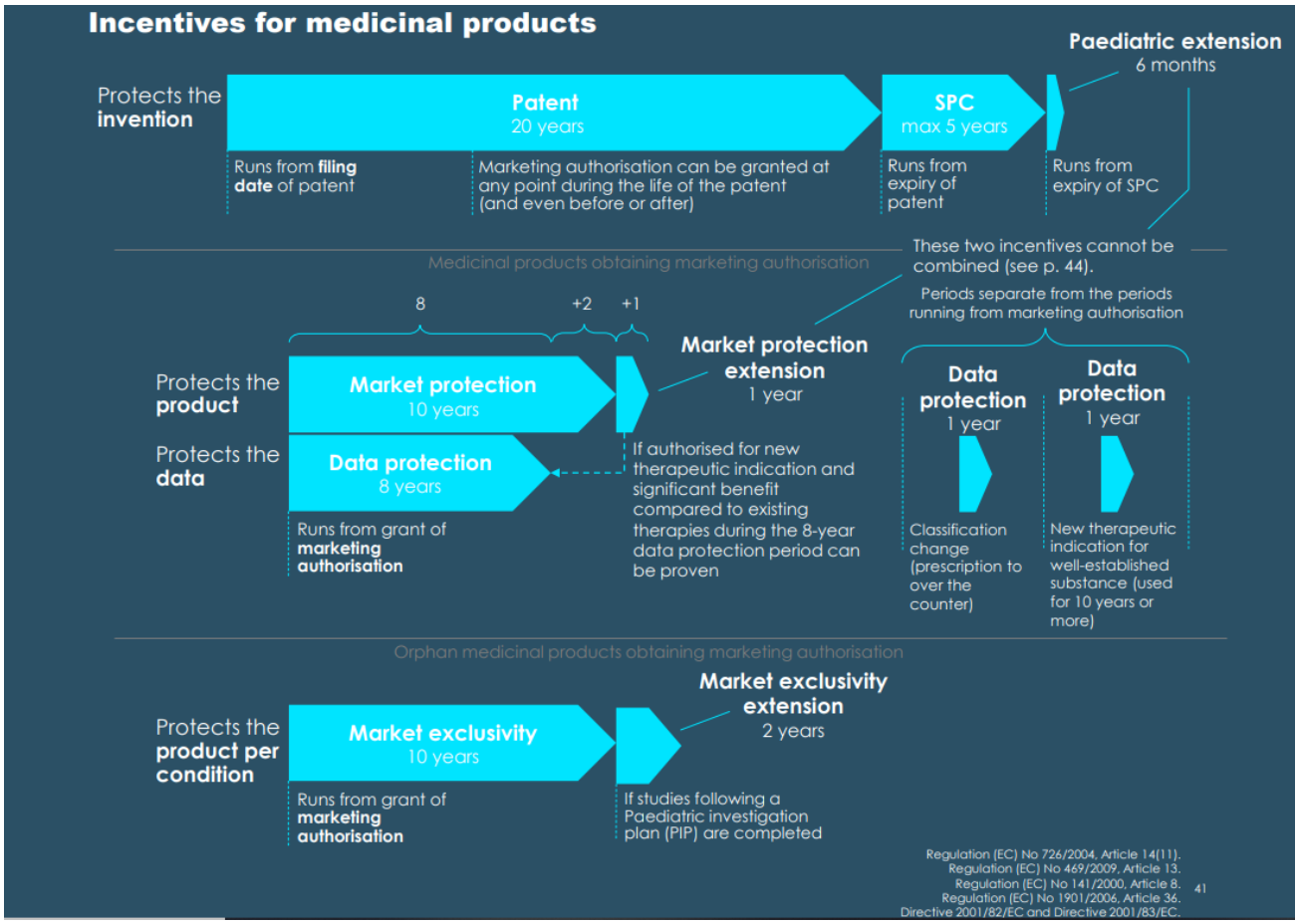
of safe, effective, people-centred and cost-effective products and services that target key unmet public health needs.

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)**[38] 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.

The diagram below provides an overview of the current IP and regulatory protection rules for medicines in the EU.



*Source: Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe - Copenhagen Economics/European Commission.

[38] 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).

The ongoing review of the SPC regulation[39] 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[40]. These decisions are influenced by the national decisions on pricing and reimbursement of the medicines concerned, since pricing and reimbursement is the competence of Members States[41].

The **Directive on transparency of measures regulating the prices of medicines** and their inclusion in the scope of national health insurance systems[42] 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**[43] 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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[39] Medicinal & plant protection products – single procedure for the granting of SPCs (europa.eu).

[40] 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 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.

[41] 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.

[42] 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).

[43] 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**[44] 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**[45] 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**[46] 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**[47] (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.

The **regulation on medical devices**[48] and **the regulation on in vitro diagnostic medical devices**[49] 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.

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[44] 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).

[45] 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).

[46] 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).

[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, 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).

[48] 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).

[49] 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 10: ANALYTICAL REPORT

The Analytical report is provided in a separate document, in attachment.

ANNEX 11: IMPACT ANALYSIS OF ALL MEASURES

The Impact analysis of all measures is provided in a separate document, in attachment.

ANNEX 12: STUDY REPORT ON IMPACT ASSESSMENT

The Study report on impact assessment is provided in a separate document, in attachment.

ANNEX 13: STUDY REPORT ON EVALUATION

The Study report on evaluation is provided in a separate document, in attachment.

ANNEX 14: 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 1. 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 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).[50] Such Joint Clinical

[50] 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.

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).[51,52,53] 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.[54] When HTA bodies consider the available clinical data inappropriate or insufficient for demonstrating an added therapeutic value, this can lead to delays and negative results in the downstream decision-making process on pricing and reimbursement.[55, 56, 57]

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.[58, 59]

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).[60]

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[51] Evidence gaps for drugs and medical devices at market entry in Europe and potential solutions - KCE (fgov.be).

[52] 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.

[53] Banzi R, Gerardi C, Bertele V, Garattini S. Conditional approval of medicines by the EMA. BMJ. 2017;357:j2062.

[54] 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.

[55] 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.

[56] Ibid, footnote 53. Banzi

[57] Ibid, footnote 54. In the interest of public health

[58] Ibid, footnote 53. Banzi

[59] Ibid, footnote 54. In the interest of public health

[60] Parallel joint scientific consultation with regulators and health technology assessment bodies | European Medicines Agency (europa.eu)

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 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).[61] In other cases, medicines became available in Central and Eastern Europe only several years after marketing authorisation[62], with market launch delayed up to three years on average in Central-Eastern Europe.[63] 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.[64]

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.

[61] 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.
[62] 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.
[63] Maini, L., & Pammolli, F., Reference Pricing as a Deterrent to Entry: Evidence from the European Pharmaceutical Market, 2017.
[64] OECD (2018), Pharmaceutical Innovation and Access to Medicines, OECD Health Policy Studies, OECD Publishing, Paris, https://doi.org/10.1787/9789264307391-en.

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.[65]

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.[66]

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.[67]

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[68] or managed entry agreements are in place (see section 2 on pricing and reimbursement

[65] Health System in Transition Reviews (HiT) (who.int)

[66] 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.

[67] 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.

[68] 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 price discounts: A survey of public and

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.*"[69]

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 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.[70] 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.

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),

statutory health systems in North America, Europe, and Australasia, Health Policy, Volume 121, Issue 4, 2017, Pages 354-362, ISSN 0168-8510.

[69] 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)

[70] Medicines Reimbursement Policies In Europe. WHO Europe. 2018

combining regulatory and HTA functions (Finland, Hungary) or combining pricing and/or reimbursement and HTA functions (Latvia, Luxembourg, Malta, Netherlands).[71]

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.[72] 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.[73] 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[74], 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 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.[75]

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

[71] Mapping of HTA national organisations, programmes and processes in EU and Norway (Study by European Commission)

[72] Euripid Guidance Document on External Reference Pricing (ERP)

[73] Access to high-priced medicines in lower-income countries in the WHO European Region

[74] 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

[75] 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).

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).[76, 77] 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[78] – around the range of 30 000 - 50 000 EUR/QALY. A debate about pros and cons is recurrent[79] – 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.[80]

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[81], France, or Italy[82]) 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.[83,84] 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,

[76] 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

[77] 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

[78] Rogalewicz, Vladimir & Barták, Miroslav. (2017). QALYs and cost-effectiveness thresholds: critical reflections.

[79] 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

[80] 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.

[81] 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

[82] Analysis on added therapeutic value of innovative pharmaceuticals by national authorities find similar results (cf. HAS statistics in France, or GRADe classification in Italy).

[83] 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)

[84] Revue Prescrire N° 448, p. 142-143

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.[85] 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.[86] Another, more fundamental reason may be that it is accepted 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. HTA-based pricing approaches reflect a choice for value-based pricing.

There is a lack of transparency on research and development costs, often triggering criticism by policymakers and stakeholders.[87] 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.[88] Although companies' annual reports provide certain insights on overall R&D spending, companies 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, as such contributions reflect risks born by the public as opposed to the investor. 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[89] 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.[90] There are two basic categories of MEAs: finance-based (such as price–volume agreements) or performance-based (based on health outcomes).[91] Confidentiality is a major feature

[85] AIMs-fair-pricing-model-Accompanying-paper-to-the-fair-pricing-calculator_June2021.pdf (aim-mutual.org)
[86] 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
[87] https://www.who.int/europe/publications/i/item/9789289058193
[88] Schipper, Irene & de Haan, Esther & Cowan, Roberta. (2019). Overpriced Drugs Developed with Dutch Public Funding.
[89] Ibid, footnote 89.
[90] 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
[91] Medicines Reimbursement Policies in Europe. 2018. https://apps.who.int/iris/bitstream/handle/10665/342220/9789289053365-eng.pdf?sequence=1&isAllowed=y

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.[92] 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."[93]

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, while freeing up funds for innovative medicines.[94] Those include – but are not limited to – incentives for prescribing biosimilars and policies related to INN prescribing, switching by physicians and substitution by pharmacists. When it comes to biosimilars, 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.[95,96] Recently, EMA and HMA published a joint statement to confirm the interchangeability of biosimilars to address this issue.[97]

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[98]. 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.[99] Looking at list price changes in markets with biosimilar competition, by 2020, biosimilars reduced the cost by almost 1/3.[100] One study estimated the impact of biosimilar entry in terms of healthcare systems savings between 2007 and 2020 for eight EU countries

[92] 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

[93] 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)

[94] 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

[95] Mestre-Ferrandiz, J., Towse, A. & Berdud, M. Biosimilars: How Can Payers Get Long-Term Savings?. *PharmacoEconomics* **34,** 609–616 (2016).

[96] 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.

[97] https://www.ema.europa.eu/en/documents/public-statement/statement-scientific-rationale-supporting-interchangeability-biosimilar-medicines-eu_en.pdf

[98] 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.

[99] https://www.pharmatimes.com/magazine/2021/may_2021/15_years_of_biosimilar_access_in_europe

[100] 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

(France, Germany, Italy, Poland, Romania, Spain, Sweden, and the UK), ranging from €11.8 billion to €33.4 billion.[101]

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.[102]

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 with ensuring access to high-priced medicines.[103] The BeNeLuxA Initiative, for instance, 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.

[101] 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.

[102] Draft final report on the Study on Best Practices in the Public Procurement of Medicines (2022), not published.

[103] In the Union, there are six such collaborations: the Baltic Procurement Initiative (May 2012, Estonia, Latvia and Lithuania); the BeNeLuxA Initiative (2015, Belgium, the Netherlands, Luxembourg, Austria (since 2016) and Ireland (since 2018)); the Fair and Affordable Pricing (FAAP) (2017, Czechia, Hungary, Poland and Slovakia); the Nordic Pharmaceutical Forum (2015, Denmark, Norway, Sweden and Iceland, Finland); the Valletta Declaration (2017, Greece, Ireland, Italy, Malta, Portugal, Romania, Spain, Cyprus (since 2017), Slovenia and Croatia (since 2018)); for details see the report Cross-country collaborations to improve access to medicines and vaccines in the WHO European Region, World Health Organization 2020.

ANNEX 15: AMR

1. Market failure hinders the commercial development of new antimicrobials[104]

The commercial success of a medicine has typically been dependent on a combination of its sales (volumes) and price. The antibiotics market suffers from a unique set of problems in these two respects. First, higher sales volumes are more likely to drive the rapid emergence of antimicrobial resistance (AMR) therefore health policies aim at reducing or delaying the use of new antimicrobials. Second, the price of antibiotics is rather low comparing to other therapeutic areas[105]. Consequently, there is lack of breakthrough candidates, new innovative antimicrobials that would slow down antimicrobial resistance (AMR)[106]. According to the World Health Organization (WHO), 11 new antibacterial medicines have been approved (by either the European Commission or Food and Drug Administration or both) since July 2017. With some exceptions, the newly approved antibiotics have limited clinical benefit over existing treatment, as over 80% (9/11) are from existing classes where resistance mechanisms are well established and rapid emergence of resistance is foreseen. The current clinical antibacterial pipeline contains 43 antibiotics and combinations with a new therapeutic entity. Only few of them meet at least one of the WHO innovation criteria (absence of known cross-resistance, new binding site, mode of action and/or class)[107]. Overall, the clinical pipeline and recently approved antibiotics are insufficient to tackle the challenge of increasing emergence and spread of antimicrobial resistance[108].

2. Push and pull incentives

To tackle this issue, a combination of **push incentives** (i.e. funding for antimicrobial R&D&I, primarily via grants that are not expected to be repaid) and **pull incentives** (i.e. financial reward for successfully developed and approved antimicrobials) is typically referred to. In May 2022, the G7 Health and Finance Ministers acknowledged the need to "address antibiotic market failure" and commit to a "particular emphasis on supporting relevant pull incentives".[109]

A financial reward to successful antimicrobial developers can notably be provided:

- In the form of **purchase of antimicrobials or purchase of a guaranteed access in the form of "reservation contract[110]"** (outcome-based pull incentives). The revenue guarantee provided by reservation of access to antimicrobials can be fully or partially delinked from sales.
- In the form of a **Transferable Exclusivity Voucher** that antimicrobial developers can sell to another marketing authorisation holder (MAH), allowing this other MAH to **extend the data protection period** of its own product. The sales value of the voucher would then provide a return on investment that is not linked with the actual sales of the antimicrobial itself.

[104] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7931625/
[105] To Push or To Pull? In a Post-COVID World, Supporting and Incentivizing Antimicrobial Drug Development Must Become a Governmental Priority (acs.org)
[106] The antibiotic subscription model: fostering innovation or repackaging old drugs? - The Lancet Microbe
[107] 2020 antibacterial agents in clinical and preclinical development: an overview and analysis (who.int)
[108] https://www.who.int/news/item/15-04-2021-global-shortage-of-innovative-antibiotics-fuels-emergence-and-spread-of-drug-resistance
[109] 2022-05-20-g7-health-ministers-communique-data.pdf (g7germany.de)
[110] The public sector and antimicrobial producers sign a service contract, through which the antimicrobial producers receive a remuneration for ensuring the availability and supply of antimicrobials, should the antimicrobials be ordered. The antimicrobials are not purchased.

Considering the high costs of bringing new antimicrobials on the market (the Boston Consulting Group estimated that a global pull incentive requires per first-to-market (in its class) antibiotic of around USD 2.5 billion over ten years), some authors consider that pull incentives should be implemented at global level. According to these authors, G7 countries, the EU, and China are responsible for 80% of global pharmaceutical sales[111], focusing on these markets offers the highest probability of success in implementing a globally aligned, sustainably sized subscription model. Under this approach, the "fair" EU contribution to pull incentive would be expected to be around USD 550 - 680 million per medicine over 10 years (considering that the EU represents around 22-27% of the GDP of the G7, EU and China).

3. Innovative financing solution - national schemes and regulatory incentives that tackle market failures for antimicrobials

In the EU, some Member States introduced national reimbursement interventions and/or other initiatives as policy tools to tackle AMR. The models seek to tie payments to antibiotic developers to the societal value of having that medicine available to the public. In return, the developer will supply the antibiotic at a volume as required. In 2018, Sweden has started a pilot project in order to ensure good availability of certain existing antibiotics via the implementation of a partially delinked guaranteed reimbursement model[112]. The key concept is that Sweden will pay at a national level the difference between actual regional sales and the guaranteed revenue[113]. Five antibiotics were chosen for this pilot. The model ensures access to existing antibacterials that have been authorised at EU/national level that may otherwise not be marketed in Sweden due to small market size. The pilot will be finalised in April 2023.

In Germany, there is an accelerated reimbursement review process and exception of antimicrobials from the internal price reference group. France also allows higher prices for certain antibacterials.

In 2020, the UK has launched a pilot project that aims to procure new, valuable antibacterials on the basis of a multi-year contract, in which the manufacturer has to provide as many doses of the antibacterial as needed in exchange to an annual guaranteed revenue[114]. The annual guaranteed revenue for each of the selected products is fully delinked from the sales and based on the HTA assessment undertaken by the National Institute for Health and Care Excellence (NICE), considering not only the direct health gain to patients treated, but additional elements such as the transmission value (the benefits of avoiding infection spread) or diversity value (the benefits of having multiple antibiotics available). Contracts will generally last for three years but may be extended up to 10 years. Currently, two antibiotics are participating in the trial - cefiderocol (Fetcroja) by Shionogi and Pfizer's ceftazidime with avibactam (Zavicefta). It is noteworthy that both antibiotics are authorised in the EU. Fetcroja[115] that belongs to the cephalosporin class of antibiotics was authorised in April 2020 and is used for complicated urinary tract infections. Zavicefta[116] received the European marketing authorisation in June 2016 and is a combination of two active substances: ceftazidime that

[111] Incentivizing Innovation to Tackle Antimicrobial Resistance | BCG
[112] Sweden to test an access-focused model for new antibiotics: Contracting for Availability • AMR.Solutions
[113] Questions and answers- Agreements signed for a pilot study of a new reimbursement model (folkhalsomyndigheten.se)
[114] https://www.england.nhs.uk/blog/how-the-nhs-model-to-tackle-antimicrobial-resistance-amr-can-set-a-global-standard/
[115] https://ec.europa.eu/health/documents/community-register/html/h1434.htm
[116] https://ec.europa.eu/health/documents/community-register/html/h1109.htm

belongs to the cephalosporin class of antibiotics and avibactam that blocks the action of bacterial enzymes called beta-lactamases.

4. International initiatives

To incentivize the creation of new treatments (antibiotics and antifungals), the US Congress enacted the Generating Antibiotic Incentives Now Act (GAIN Act)[117] of 2012, which provides benefits to manufacturers of Qualified Infectious Disease Products (QIDPs) including 5 years of additional non-patent exclusivity. For QIDP designation, the sponsor is required to demonstrate that the drug is an "antibacterial or antifungal drug for human use intended to treat serious or life-threatening infections"[118]. The results of this program have so far been disappointing, largely because QIDP eligibility criteria were not sufficiently targeted to unmet need[119].

The US does not currently have a subscription model for antibiotics in place. However, the PASTEUR (Pioneering Antimicrobial Subscriptions to End Upsurging Resistance) Act[120] is currently under discussion (timelines not known). It aims to implement a de-linked subscription model to boost novel antimicrobial development, encourage the appropriate use of existing drugs, and safeguard a domestic supply. It would provide the guaranteed payments from the federal government to developers ranging between $750 million to $3 billion for "unlimited access" to an antibiotic, paid out over five to 10 years. The budget of the PASTEUR Act would be $11 billion over 10 years (including $500 million for stewardship programs), with the goal of financing between three and 14 contracts, depending on their value.

On-going financial initiatives

Further to the above-mentioned incentives, several funding initiatives support the antibiotic development via push incentives:

- activities under DG RTD in Europe including the Innovative Medicines Initiatives (IMI)[121] and IMI2[122];
- AMR Action Fund[123] (worldwide collaboration between the pharmaceutical industry, WHO, EIB and Wellcome Trust);
- The Biomedical Advanced Research and Development Authority (BARDA)[124] in the US;
- The Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator known as the CARB-X[125] (a global nonprofit public-private partnership).

[117] GENERATING ANTIBIOTIC INCENTIVES NOW (fda.gov)
[118] Qualified Infectious Disease Product Designation Questions and Answers | FDA
[119] https://academic.oup.com/ofid/article/7/1/ofaa001/5716891
[120] H.R.8920 - 116th Congress (2019-2020): The PASTEUR Act | Congress.gov | Library of Congress
[121] https://www.imi.europa.eu/projects-results/project-factsheets/nd4bb
[122] https://www.imi.europa.eu/projects-results/project-factsheets/amr-accelerator
[123] AMR Action Fund Announces First Investments in Adaptive Phage Therapeutics and Venatorx Pharmaceuticals
[124] https://www.phe.gov/about/barda/Pages/AMR.aspx
[125] https://carb-x.org/

5. Future initiatives

The EU co-funded Joint Action on AMR and Health Care Associated Infections (EU JAMRAI) developed **a multi-country pull incentive strategy**[126].

The EU-JAMRAI strategy is based on two key elements: (i) A **guaranteed revenue** paid to antimicrobial producers **for ensuring access** to antimicrobials (i.e. subscription model[127]) **through national contracts;** (ii) A **supranational entity** - **coordinating** the implementation of the subscription models.

A supranational entity launches a joint open tender, which:

- specifies eligible antimicrobial characteristics in coordination with relevant global stakeholders, e.g. EMA, EC bodies, World Health Organization (WHO) and national competent authorities and,
- encompasses a contract template including national access and stewardship requirements as well as a suggested revenue guarantee (which is up to negotiation between national authorities and the pharmaceutical industry). The annual guaranteed revenue can be either partially or fully delinked from the volume-based sales.

Marketing authorisation holders apply for the tender. Once the tender participants are agreed, each country negotiates individually with the marketing authorisation holder and ultimately enters into a contract. National authorities commit to guarantee a certain revenue to the antimicrobial producer(s) in exchange to ensuring sustainable access to antimicrobials.

DG HERA could implement the EU-JAMRAI proposal through the organisation of a joint procurement where Member States would buy a guaranteed access to existing antimicrobials (service contract) for a given volume and period. The joint procurement could target either newly approved antimicrobials, and/or old antimicrobials which are not available in all EU Member States. In both cases, the incentive will provide access, but may not be big enough to incentivise innovation.

6. Prudent use of antimicrobials

Infections caused by antibacterial drug-resistant bacteria are an important public health threat in Europe and worldwide. New treatment alone will not be sufficient to combat the threat of AMR. It is well known that AMR is accelerated by the misuse and overuse of antimicrobials[128]. The prudent use of antimicrobials is a cornerstone in addressing antimicrobial resistance. The revision of the pharmaceutical legislation will not only restrict the use of antimicrobial by introducing the prescription status for all antimicrobials for systemic use, but also to oblige industry to closely follow its products and possible implications on AMR through the AMR lifecycle management plan. The proposed enhanced environmental risk assessment and imposition of relevant risk minimisation measures on the manufacture, use and disposal of antimicrobials will also contribute to reducing AMR though the environment.

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126 https://eu-jamrai.eu/wp-content/uploads/2021/03/EUjamrai_D9.2_Strategy-for-a-multi-country-incentive-in-Europe_INSERM-FHI.pdf

127 Sweden and UK currently implement subscription models as pilot studies for a small selected number of antibiotics. In the Swedish model, the revenue is partially delinked from the sales, while in the UK model, the revenue is fully delinked. Both models ensure access to existing antibacterials that may otherwise not be marketed, but may not be large enough to substantially incentivise antibacterial R&D. The first impact assessments of the Swedish model are expected to be shared in November 2022.

128 Antimicrobial resistance (who.int)

ANNEX 16: MAPPING MEASURES AGAINST PROBLEM DRIVERS

Measure	Problem driver/problem
Reduce standard regulatory protection period	Expensive innovative medicines
Market launch measure	Medicines not launched in the EU Companies do not initiate negotiations for pricing or reimbursement
Prolonged regulatory protection for medicines addressing UMN	High commercial risk to develop and introduce new medicines addressing UMN
Transparency of public financial support to conduct clinical trials	Expensive innovative medicines
Regulatory protection for comparative trials	Evidence for HTA/pricing and reimbursement bodies not generated
Changes to scope, definition, classification advice and codification of rolling review and PRIME Sandbox environment	System caters insufficiently for innovation Framework lacks agility
Binding system for scientific assessment for repurposed medicines	High commercial risk to develop and introduce new medicines addressing UMN
Simplified obligations for non-commercial entities to become MAH	High commercial risk to develop and introduce new medicines addressing UMN
Strengthened Bolar provision	Expensive innovative medicines Delayed market entry for generics and biosimilars
Transferable exclusivity voucher for novel antimicrobials	Limited income and profit for MAHs of these products
Prudent use of antimicrobials	Inappropriate use of these products
Measure on shortages and security of the supply chain	Withdrawals of medicines Vulnerability of the supply chain Patients without treatments
Strengthened ERA requirements	Insufficient regulation
Stronger oversight of manufacturing supply chains	Vulnerability of the supply chain
Simplification and streamlining measures	Inefficiencies in the system
Measures regarding novel combination products	System caters insufficiently for innovation
New concepts, e.g. adaptive clinical trials and use of real world evidence	System caters insufficiently for innovation
Electronic product information	Inefficiencies in the system Shortages
Adapted working methods of EMA and European Medicines Regulatory Network	Inefficiencies in the system
Early dialogue, coordinated scientific advice	Evidence for HTA/pricing and reimbursement bodies not generated System caters insufficiently for innovation