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COMMISSION STAFF WORKING DOCUMENT

IMPACT ASSESSMENT REPORT

Accompanying the documents

Proposal for a Directive of the European Parliament and of the Council on the Union code relating to medicinal products for human use, and repealing Directive 2001/83/EC and Directive 2009/35/EC

Proposal for a Regulation of the European Parliament and of the Council laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, amending Regulation (EC) No 1394/2007 and Regulation (EU) No 536/2014 and repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006

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GLOSSARY

Term or acronym	*Meaning or definition*
Accessibility	A medicine becomes accessible to patients once it has been authorised, is being marketed, and can be reimbursed in a Member State.
Affordability	Relates to payments to be made by patients (out of pocket on healthcare or through co-payments) which can be described as affordability at micro level and to the sustainability of public funding of the healthcare sector raised through social security contributions or taxes (affordability at macro level).
AMR	Antimicrobial resistance.
Antibacterial/antibiotic	Any substance with a direct action on bacteria that is used for treatment or prevention of infections or infectious diseases.
Antimicrobial	Any substance with a direct action on micro-organisms used for treatment or prevention of infections or infectious diseases, including antibiotics, antivirals, antifungals and anti-protozoals.
Antimicrobial resistance (AMR)	The ability of micro-organisms to survive or to grow in the presence of a concentration of an antimicrobial agent which is usually sufficient to inhibit or kill micro-organisms of the same species.
API	Active Pharmaceutical Ingredient.
ATC	Anatomical Therapeutic Chemical code.
Conditional marketing authorisation	Conditional marketing authorisation is the approval to market a medicine that addresses patients' unmet medical needs on the basis of data that is less comprehensive than that normally required. The available data must indicate that the medicine's benefits outweigh its risks and the applicant should be in a position to provide comprehensive clinical data in the future.

CMDh	The Coordination Group for Mutual recognition and Decentralised Procedures – Human is EMA's committee responsible for the examination and coordination of questions relating to the marketing authorisation of human medicines in two or more Member States in accordance with the mutual recognition or decentralised procedure.
COM	European Commission.
COMP	The Committee for Orphan Medicinal Products is the Agency's committee responsible for recommending orphan designation of medicines for rare diseases.
CP	The centralised authorisation procedure is the European Union-wide procedure for the authorisation of medicines, where there is a single application, a single evaluation and a single authorisation granted by the European Commission valid throughout the EU.
Data protection	Period of protection during which pre-clinical and clinical data and data from clinical trials handed in to the authorities by one company cannot be referenced by another company in their regulatory filings.
DCP	The decentralised procedure is the procedure for authorising medicines in more than one European Union Member State in parallel. It can be used for medicines that do not need to be authorised via the centralised procedure and have not already been authorised in any Member State. The DCP was introduced by Directive 2004/27/EC, by the 2004 revision.
EEA	The European Economic Area includes all EU Member States and also Iceland, Liechtenstein and Norway.
EMA	The European Medicines Agency ('the Agency') is an EU agency founded in 1995 which is responsible for the scientific evaluation, supervision and safety monitoring of medicines, both human and veterinary, across the EU.
ERA	Environmental Risk Assessment
EU	European Union.
EudraVigilance	A centralised European database of suspected adverse

	reactions to medicines that are authorised or being studied in clinical trials in the European Economic Area (EEA).
Evergreening	'Evergreening' strategies extend the effective patent period and thus allow drug companies to maintain a market share after their drug patents expire by introducing "follow-on drugs" – those with slight changes made to them after expired patents allow generic competitors to enter the market.
FDA	United States Food and Drug Administration.
GDP	Good Distribution Practices.
GDPR	General Data Protection Regulation.
GMP	Good Manufacturing Practices.
GMO	Genetically Modified Organism.
Generic medicine	A generic medicine contains the same active substance(s) as the reference medicine, and it is used at the same dose(s) to treat the same disease(s). The generic can only be marketed after expiry of the data and market protection of its reference medicine.
HTA	Health Technology Assessment is a multidisciplinary process that summarises information about the medical, patient and social aspects and the economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased and robust manner.
HUMN	High Unmet Medical Need
IA	An impact assessment identifies and describes the problems to be tackled, establishes objectives, formulates policy options, assesses the impacts of these options and describes how the expected results will be monitored. The Commission's impact assessment system follows an integrated approach that assesses the environmental, social and economic impacts of a range of policy options.
ICER	An incremental cost-effectiveness ratio is a summary measure representing the economic value of an intervention, compared with an alternative (the comparator). An ICER is calculated by dividing the difference in total costs (incremental cost) by the difference in the chosen measure of health outcome or effect (incremental effect) to provide a ratio of 'extra cost per extra unit of health effect' for the more

	expensive therapy versus the alternative.
IP	Intellectual property
IQVIA	IQVIA is a contract research and analytical services organisation that collects data including global pharmaceutical sales data.
Killer acquisitions	'Killer acquisitions' is used as shorthand for: 'acquisitions' (in a wide economic sense) of innovative competitors which have as their object or effect the discontinuation of overlapping R&D projects to the detriment of innovation competition and ultimately consumers. Cunningham, C., Ederer, F. and Ma, S. (2021), "Killer acquisitions", Journal of Political Economy, Vol. 129, No. 3, pp. 649–702. 2
MA	A marketing authorisation is the mandatory approval process before a medicine enters the market of one, several or all EU Member States.
MAH	Marketing authorisation holder
Marketing authorisation application	An application made to a European regulatory authority for approval to market a medicine within the EU.
Marketing authorisation grant	A decision granting the marketing authorisation issued by the relevant authority.
Market exclusivity	The period after the marketing authorisation of a medicine for a rare disease when similar medicines for the same indication cannot be placed on the market and applications for those medicines cannot be validated. Under the current legislation, the market exclusivity has a duration of 10 years.
Market protection	Period of protection during which generics cannot be placed on the market.
MDGs	The United Nations Millennium Development Goals are 8 goals that UN Member States have agreed to try to achieve by the year 2015 to reduce extreme poverty. The MDGs have been superseded by the United Nations Sustainable Development Goals.
Medical condition	Any deviation(s) from the normal structure or function of the body, as manifested by a characteristic set of signs and symptoms (typically a recognised distinct disease or a syndrome).
Megatrend	Megatrends are long-term driving forces that are observable now and will most likely have significant

	influence on the future. Megatrends are closely interlinked between each other and simultaneously affect many different stakeholders. Thus, a systemic and global understanding of the issue under study is necessary to fully picture and illustrate the dynamics at stake. See also: The Megatrends Hub | Knowledge for policy (europa.eu)
MRP	The mutual recognition procedure (MRP) is a procedure through which an authorisation of a medicine in one EU Member State is recognised by another Member State.
MS	Member States are countries member of the EU.
National authorisation procedure	The national authorisation procedure is a marketing authorisation procedure where individual Member States authorise medicines for use in their own territory. This procedure depends on national legislation.
NAS	New active substances.
NCA	National Competent Authority.
NCE	New Chemical Entity.
"Off-label" use	Use of a medicine for an unapproved indication or in an unapproved age group, dosage, or route of administration.
Oncology	A branch of medicine that specialises in the prevention, diagnosis and treatment of cancer.
Orphan designation	A status assigned to a medicine intended for use against a rare condition. The medicine must fulfil certain criteria for designation so that it can benefit from incentives such as market exclusivity.
Parallel import	Parallel import/trade is based on the principle of free movement of goods in the internal market (TFEU Articles 34 and 36). This trade is known as "parallel" to the extent that it takes place outside and – in most cases – in parallel with the distribution network that the manufacturers or original suppliers have established for their products.
Payer	An entity responsible for financing or reimbursing healthcare.

PDCO	The Paediatric Committee is EMA scientific committee responsible for activities associated with medicines for children. It supports the development of such medicines in the EU by providing scientific expertise and defining paediatric need.
Personalised medicine	A medical model using characterisation of individuals' phenotypes and genotypes (e.g. molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention.
Pharmacovigilance	The monitoring of the safety of an authorised medicine and the detection of any change to its benefit-risk balance.
PIP	A paediatric investigation plan is a development plan designed to ensure that the data required to support the authorisation of a paediatric medicine are obtained through studies of its effect on children.
PRIME	The priority medicine scheme has been launched by the European Medicines Agency to enhance support for the development of medicines that target an unmet medical need. Through this voluntary scheme the Agency offers early and proactive support to medicine developers to optimise the generation of robust data on a medicine's benefits and risks, to optimise development plans and to enable accelerated assessment of applications.
QALYs	Quality-adjusted life years refers to a measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to one year of life in perfect health. QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality-of-life score (on a 0 to 1 scale). It is often measured in terms of the person's ability to carry out the activities of daily life and freedom from pain and mental disturbance.
Rare disease	Diseases with a particularly low prevalence. The EU considers diseases to be rare when they affect no more than 5 per 10,000 people in the EU.
Repurposed medicines	Medicines repurposing identifies new uses for licensed medicines that are outside of the scope of the originally intended use for the medicine. This typically involves taking an existing medicine that already has a marketing authorisation or licence for human use for a

	particular condition, and then using it to treat another condition. Alternatively, a repurposed medicine may be used in a different dose, or form, than its original licence (for example an inhaled product, rather than a tablet).
RSB	The Regulatory Scrutiny Board is an independent body of the Commission that offers advice to the College of Commissioners. It provides a central quality control and support function for the Commission's impact assessment and evaluation work. The Board examines and issues opinions and recommendations on all the Commission's draft impact assessments and its major evaluations and fitness checks of existing legislation.
Repeat use procedure (RUP)	Repeat Use Procedure is the use of the Mutual Recognition Procedure (MRP) after the completion of a first MRP or Decentralised Procedure (DCP) for the recognition of a marketing authorisation by other Member States.
SA	A scientific advice (SA) is the provision of advice by the Agency on the appropriate tests and studies required in developing a medicine, or on the quality of a medicine.
SDGs	The United Nations Sustainable Development Goals (UN SDGs) are 17 goals with 169 targets that all UN Member States have agreed to work towards achieving by the year 2030. They set out a vision for a world free from poverty, hunger and disease.
SmPC	A summary of product characteristics (SmPC) describes the properties and the officially approved conditions of use of a medicine.
SMEs	Micro, small and medium-sized enterprises.
SPC	The supplementary protection certificate is an intellectual property right that serves as an extension to a patent right. The patent right extension applies to specific pharmaceutical and plant protection products that have been authorised by regulatory authorities.
SWD	Staff working documents are required to present the results of all impact assessments and evaluations/fitness checks.
Therapeutic indication	The proposed indication for the marketing authorisation. A medical condition that a medicine is used for. This can include the treatment, prevention and diagnosis of a disease. The therapeutic indication

	granted at the time of marketing authorisation will be the result of the assessment of quality, safety and efficacy data submitted with the marketing application.
UMN	Unmet medical need - see Annex 6 for possible criteria for unmet medical need.

1 INTRODUCTION: POLITICAL AND LEGAL CONTEXT

This impact assessment covers Directive 2001/83/EC[1] and Regulation (EC) No 726/2004[2] ("general pharmaceutical legislation"). The EU general pharmaceutical legislation was established in 1965 with the dual objective of safeguarding public health and harmonising the internal market for medicines. It has developed considerably since then, but these overarching objectives have guided all revisions. The general pharmaceutical legislation is complemented by the *specialised* legislation for medicines for rare diseases ('Orphan Regulation')[3], medicines for children ('Paediatric Regulation')[4], currently under revision, and advanced therapy medicines ('ATMP Regulation')[5]. The general legislation applies to these specialised medicines, while the specialised frameworks provide additional measures to address their specific characteristics. In particular, they address market failures by providing specific *incentives* for development of medicines for small number of patients affected by rare diseases and *rewards* for companies that fulfil the *obligation* to screen adult medicines under development for use in children[6]. The ATMP regulation adapts the technical requirements for the authorisation of medicines based on genes, tissues or cells.

The general pharmaceutical legislation governs the granting of marketing authorisations for all medicines for human use by defining conditions and procedures to enter and remain on the market. A fundamental principle is that a marketing authorisation is granted only to medicines with a positive benefit-risk balance after assessment of their quality, safety and efficacy.

The most recent comprehensive revision took place in 2004 while targeted revisions on post-authorisation monitoring (pharmacovigilance)[7] and on falsified medicines[8] were adopted subsequently. In the almost 20 years since this revision, the pharmaceutical sector has changed and has become more globalised, both in terms of development and manufacture. The roles of 'big pharma' and SMEs have changed, with emerging biopharma companies – often SMEs – increasingly driving innovation and development, with these developments taken over by 'big pharma' through acquisitions or licence agreements.[9] Science and technology have evolved at a rapid pace. However, there continues to be unmet medical needs[10], i.e. diseases without or only with suboptimal treatments. Moreover, some patients may not benefit from innovation because medicines may be unaffordable or not launched (i.e. placed on the market) in the Member State concerned. There is

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

[2] Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing a European Medicines Agency, OJ L136, 30.4.2004, p.1.

[3] Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products

[4] Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004

[5] Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004

[6] See Annex 6 for further details on the coherence between the two initiatives.

[7] Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use, OJ L 348, 31.12.2010, p. 74, and Directive 2012/26/EU of the European Parliament and of the Council of 25 October 2012 amending Directive 2001/83/EC as regards pharmacovigilance, OJ L 299, 27.10.2012, p. 1.

[8] Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of entry into the legal supply chain of falsified medicinal products, OJ L 174, 1.7.2011, p. 74.

[9] See Annex 9 for further description of the pharmaceutical ecosystem.

[10] Possible criteria to define unmet medical need are described in Annex 6.

also a greater awareness of the environmental impact of medicines. More recently, the COVID-19 pandemic has stress tested the framework.

This impact assessment (IA) analyses policy options designed to address shortcomings highlighted in the evaluation[11] of the general pharmaceutical legislation, taking into account the lessons learnt from the COVID-19 pandemic. It was conducted in parallel with the evaluation (a 'back-to-back' exercise).

The revision is part of the implementation of the Pharmaceutical strategy for Europe[12] and aims to:

- Promote innovation, in particular for unmet medical needs, while reducing regulatory burden and the environmental impact of medicines;
- Ensure access to innovative and established medicines for patients, with special attention to enhancing security of supply and addressing risks of shortages, taking into account the challenges of the smaller markets of the EU;
- Create a balanced and competitive system that keeps medicines affordable for health systems while rewarding innovation.

This revision focuses on provisions relevant to achieve its specific objectives; therefore it covers all but provisions concerning advertising, falsified medicines, homeopathic and traditional herbal medicines. The revision of the general pharmaceutical legislation will be presented as a 'package' with the revision of the orphan and paediatric legislation. The ATMP regulation is not revised, but the revision of the general legislation will address some of the issues, e.g. broad application of hospital exemption, innovative or specific manufacturing methods for these products and burdensome procedures, identified[13] through the experience accumulated since the entry into force of the ATMP Regulation and will help translate research into ATMPs available to patients across the EU while maintaining a high level of public health protection.

1.1 Political context

Since the 2004 revision of the general pharmaceutical legislation, certain aspects such as unequal patient access, affordability, shortages, or the environmental impact of medicines have become more prominent and moved up the political agenda. This is evidenced by recent Council conclusions[14] and resolutions of the European Parliament[15] which called for a balanced system of incentives, rewarding innovation while improving access. Member States called for revised mechanisms and incentives for medicines development tailored to the level of unmet medical need, while ensuring patient access and availability of medicines in all Member States. The COVID-19 pandemic has spotlighted some critical issues in the European pharmaceutical policy.

The Pharmaceutical strategy for Europe[16] – adopted in November 2020 – is an important building block of the European Health Union[17] and more than a response to the pandemic. The strategy is a holistic answer to the current challenges of the pharmaceutical policy with 55 legislative and non-

[11] Annex 5.
[12] COM(2020) 761 final.
[13] COM(2014) 188 final.
[14] Council conclusions on strengthening the balance in the pharmaceutical systems in the EU and its Member States, OJ C, C/269, 23.07.2016, p. 31. Strengthening the European Health Union: improving accessibility to and availability of medicinal products and medical devices. Council Conclusions on Access to medicines and medical devices for a Stronger and Resilient EU, (2021/C 269 I/02).
[15] European Parliament resolution of 2 March 2017 on EU options for improving access to medicine (2016/2057(INI)) Shortages of medicines, 2020/2071(INI).
[16] COM(2020) 761 final https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe_en
[17] COM(2020) 724 final, available at https://ec.europa.eu/info/strategy/priorities-2019-2024/promoting-our-european-way-life/european-health-union_en.

legislative actions interacting together to achieve its overall goal of ensuring Europe's supply of safe and affordable medicines and supporting the European pharmaceutical industry's innovation efforts[18]. The revision of the general pharmaceutical legislation and the ongoing revision of the legislation on medicines for children and rare diseases[19] are flagship initiatives of the strategy. Although the revision of the general pharmaceutical legislation is a key element in addressing the objectives of the strategy, its effect needs to be seen with the other actions of the strategy, actions under EU4Health[20] and other relevant EU and national policies.

The **research and development stage** for medicines is supported by Horizon Europe[21] – a key funding programme for EU research and innovation – as well as the Innovative Health Initiative[22], co-funded by Horizon Europe, to promote innovation of medicines, including planned, specific partnerships to address unmet medical need[23] and AMR[24]. The Mission on Cancer[25], together with Europe's Beating Cancer Plan[26] will allow to better support development of cancer treatments. The budget for health research under Horizon Europe amounts to €8.2bn[27]; additional health research is funded by national programmes. In 2016, Member States from which data are available collectively budgeted about €11.3bn for health-related R&D; this figure excludes most tax incentives and funding for higher education and publicly-owned corporations[28]. In the EU, private investment in R&D in medicines and biotechnology has doubled from around €20bn in 2000 to more than €40bn in 2018; in the US, starting from a higher level at €40bn it almost doubled to around €75bn in the same period[29].

The European Health Data Space[30]- under the European strategy for data[31] – will provide a common framework across Member States for access to high-quality real world health data. Use of these will allow progress in research and development of medicines and provide new tools for pharmacovigilance. The revision of the general pharmaceutical legislation will better accommodate **digital tools and the use of health data** fitting the ambitions of 'Shaping Europe's Digital Future'[32]

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[18] mission-letter-stella-kyriakides_en.pdf (europa.eu)
[19] Medicines for children & rare diseases – updated rules, available at https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12767-Medicines-for-children-rare-diseases-updated-rules_en.
[20] E.g. a joint action to support the cooperation between competent authorities by organising trainings, improving scientific assessment capacities and inspections, and an action to contribute to implement the Pharmaceutical Strategy as it concerns supporting Member States in national pricing and reimbursement policies.
[21] Regulation (EU) 2021/695 of the European Parliament and of the Council of 28 April 2021 establishing Horizon Europe – the Framework Programme for Research and Innovation, laying down its rules for participation and dissemination, and repealing Regulations (EU) No 1290/2013 and (EU) No 1291/2013, OJ L 170, 12.5.2021, p. 1.
[22] Council Regulation (EU) 2021/2085 of 19 November 2021 establishing the Joint Undertakings under Horizon Europe and repealing Regulations (EC) No 219/2007, (EU) No 557/2014, (EU) No 558/2014, (EU) No 559/2014, (EU) No 560/2014, (EU) No 561/2014 and (EU) No 642/2014, OJ L427, 30.11.2021, p. 17.
[23] European Partnership on Rare Diseases will develop a European Clinical Research Network to accelerate clinical trials for rare diseases; support access to data, information resources to translate research results into safe and effective medicines; support the scientific work of the International Rare Disease Research Consortium; and integrate basic, pre-clinical and clinical research. This partnership is planned for the work programme 2023/4.
[24] European Partnership: One Health Anti-Microbial Resistance will contribute to achieving the objectives of the European One Health Action Plan against AMR[24] and the World Health Organization Global Action Plan on AMR[24], by reducing the threat of AMR and contribute to achieving the objectives of the Health Emergency Preparedness and Response Authority (HERA). This partnership is planned for the work programme 2023/4.
[25] EU Mission: Cancer, available at EU Mission: Cancer | European Commission (europa.eu)
[26] COM/2021/44 final.
[27] European Commission, Directorate-General for Research and Innovation, *Horizon Europe, budget: Horizon Europe - the most ambitious EU research & innovation programme ever*, 2021, https://data.europa.eu/doi/10.2777/202859.
[28] OECD, Pharmaceutical Innovation and Access to Medicines, OECD Health Policy Studies, 2018.
[29] Analytical report, indicator RI-8, Annex 10.
[30] COM(2022) 197 final.
[31] COM(2020) 66 final.
[32] COM(2020) 67 final.

and the digital transition. By facilitating access to and use of health data the two initiatives together will support the **competitiveness and innovation capacity** of the EU's medical industry.

In 2021, the Health Emergency Preparedness and Response (HERA) was created in the aftermath of the COVID-19 pandemic to prevent, detect and rapidly respond to health emergencies. While HERA can address medicines shortages related to a health emergency, it will not play a role in addressing the challenges of **systemic shortages** targeted by the revision of the general pharmaceutical legislation.

The European One Health Action Plan against **Antimicrobial Resistance** (AMR)[33] aims to reduce AMR and develop alternative treatments or prevent diseases treated with antimicrobials. The revision of the general pharmaceutical legislation would contribute to the implementation of this action plan, together with the planned Council Recommendation on AMR.

The revision will also address **environmental challenges** together with European Green Deal[34] initiatives such as: the EU Action Plan "Towards a Zero Pollution for Air, Water and Soil"[35], the revision of the Urban Waste Water Treatment Directive[36], the revision of the Industrial Emissions Directive[37] and the revision of the list of surface and groundwater pollutants[38] under the Water Framework Directive[39] to include some medicines in order to protect the environment and the public health. Moreover, the EU Strategic Approach to Pharmaceuticals in the Environment[40] lists measures to address challenges from medicine residues.

Finally, this initiative supports the United Nations' **Sustainable Development Goals** (SDGs)[41] and in particular SGD 3 ('ensure healthy lives and promote well-being for all at all ages'), SDG 9 ('build resilient infrastructure, promote inclusive and sustainable industrialisation and foster innovation') and SDG 10 ('reduced inequalities'). The objectives and proposed measures relating to unmet medical need, affordability and unequal access to medicines across the EU are linked to SDG 3 and SDG 10, while those relating to environmental challenges and addressing inefficiencies of the regulatory system contribute to SDG 9.

1.2 Legal context

Directive 2001/83/EC and Regulation (EU) No 726/2004 form one policy intervention, the 'general pharmaceutical legislation' that regulates the authorisation, manufacturing, distribution and monitoring of medicines. It also provides regulatory protection periods to reward innovative medicines.[42] The legislation is based on cooperation and division of responsibilities between the EU and Member States. It provides for common standards but different pathways for an authorisation at EU and at Member State level.[43] Member States are responsible for the authorisation of manufacturers and wholesale distributors and they conduct inspections of companies.

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[33] A European One Health Action Plan against Antimicrobial Resistance (AMR) (June 2017).
[34] COM (2019) 640 final.
[35] COM/2021/400 final
[36] Council Directive 91/271/EEC of 21 May 1991 concerning urban waste-water treatment, OJ L 135, 30.5.1991, p. 40.
[37] Directive 2010/75/EU of the European Parliament and of the Council of 24 November 2010 on industrial emissions (integrated pollution prevention and control, OJ L 334, 17.12.2010, p. 17, and COM(2022) 156 final.
[38] Integrated water management – revised lists of surface and groundwater pollutants (europa.eu).
[39] Directive 2000/60/ EC of the European Parliament and of the Council of 23 October 2000 establishing a framework for Community action in the field of water policy, OJ L 327, 22.12.2000
[40] COM(2019) 128 final.
[41] Home - United Nations Sustainable Development
[42] These regulatory protection periods are described in section 6.1 and in the evaluation SWD, section 3.3, Annex 5.
[43] For certain categories of medicines it is a requirement and for others it is an option for companies to apply for a marketing authorisation granted by the European Commission through the centralised procedure. This authorisation is valid in all Member States and based on a scientific assessment performed by the EMA. Medicines may also be authorised through national procedures. The different authorisation procedures are outlined in Annex 7.

Pharmacovigilance is a shared responsibility. The legislation does not affect the Member States' powers regarding the setting of medicine prices or the inclusion of medicines in the scope of national health insurance schemes.

The general pharmaceutical legislation has touchpoints with other legislation. The ongoing revision of the legislation on medicines for rare diseases and medicines for children is coherent with this revision in it aims to address unmet medical needs and improve patient access to medicines; a description of how the initiatives complement each other can be found in Annex 6.

The Clinical Trials Regulation[44], applicable since 2022, allows a more efficient approval of clinical trials in the EU, while the extended EMA mandate, as part of the European Health Union, strengthens the role of the Agency for a coordinated EU-level response to health crises[45] to ensure access to medicines in such crisis. The EMA fees legislation[46] is currently under revision. The fees support EMA and national competent authorities and contribute to the sustainability of the EU regulatory system.

The revision of the EU legislation on blood, tissues and cells (BTC)[47] is relevant as some substances of human origin are starting materials for medicines. Coherence between the two revisions is key to ensure clarity as to which legislation applies to some BTC based therapies.

For **access to medicines**, in addition to the general pharmaceutical legislation, the intellectual property frameworks (patents and SPCs) as well as the HTA Regulation and the 'Transparency' Directive[48] play a role. The Intellectual Property Action Plan[49] under the Industrial Strategy[50] includes the modernisation of the system of supplementary protection certificates (SPC) in the form of a "Unitary SPC" which does not intend to modify the maximum period of a SPC, but may lead to wider coverage of the SPCs; an impact assessment on these changes is under development.[51] SPCs extend patent rights to protect **innovation** and compensate for lengthy clinical trials and marketing authorisation procedures. At the same time, they impact the effect of regulatory protection periods provided by the pharmaceutical legislation and therefore the entry of generic and biosimilar medicines and eventually **patient access to medicines and affordability**. Member States' decisions on pricing and reimbursement of medicines also influence access. The 'Transparency' Directive regulates procedural aspects of the Member States' pricing and reimbursement decisions but do not

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

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

[46] Council Regulation (EC) No 297/95 of 10 February 1995 on fees payable to the European Agency for the Evaluation of Medicinal Products, OJ L 35, 15.2.1995, p. 1, and Regulation (EU) No 658/2014 of the European Parliament and of the Council on fees payable to the European Medicines Agency for the conduct of pharmacovigilance activities in respect of medicinal products for human use, OJ L 189, 27.6.2014, p. 112. These regulations set out fee amounts and allows for remuneration of the national competent authorities for the contributions to services provided by EMA to companies, e.g. assessment of application for marketing authorisation.

[47] Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC, OJ L 33, 8.2.2003, p. 30, and Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, OJ L 102, 7.4.2004, p. 48.

[48] Council Directive 89/105/EEC, of 21 December 1998, relating to the transparency of measures regulating the pricing of medicinal products for human use and their inclusion in the scope of the national health insurance systems, OJ L 40, 11.2.89, p. 8.

[49] COM(2020) 760 final.

[50] COM(2021) 350 final.

[51] Medicinal & plant protection products – singles procedure for the granting of SPCs

impact on the level of price. The Health Technology Assessment (HTA) Regulation[52] will engage national HTA bodies in joint clinical assessment to provide evidence-based information on the comparative effectiveness of medicines to help national decisions on pricing and reimbursement. This contributes to improve affordability and access across the EU. Annex 14 further describes the multiplicity of factors having an impact and framing access to affordable medicines.

A description of the pharmaceutical ecosystem and legislative landscape can be found in Annex 9 together with a visual overview of the lifecycle of a medicine in Annex 8.

2 PROBLEM DEFINITION

2.1 What are the problems?

The evaluation of the general pharmaceutical legislation showed that the legislation continues to be relevant for the dual overarching objectives of protection of public health and harmonisation of the internal market for medicines in the EU. The legislation delivered on the objectives of the 2004 revision; albeit not to the same extent for all. The objective to ensure quality, safety and efficacy of medicines was achieved to the largest extent, while patient access to medicines in all Member States was achieved only to a limited extent. As to ensuring the competitive functioning of the internal market and attractiveness in a global context, the legislation has performed to a moderate extent. The evaluation found that the achievements or shortcomings of the 2004 revision vis-a-vis its objectives depend on many external factors outside the remit of the legislation, e.g. R&D activities and international location of R&D clusters, national pricing and reimbursement decisions, business decisions and market size. The pharmaceutical sector and development of medicines are global; research and clinical trials conducted on one continent will support development and authorisation in other continents; likewise the supply chains and manufacturing of medicines are global. International cooperation to harmonise requirements to support authorisation exists, e.g. the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. The evaluation identified six shortcomings which are not adequately addressed by the pharmaceutical legislation recognising that they also depend on factors outside its remit:

Medical needs of patients are not sufficiently met

The evaluation showed that the legislation has been less relevant to ensure development of medicines addressing unmet medical needs, including novel antimicrobials. This related to e.g. lack of adequate incentives for innovation by SMEs, academic/industry collaborations. Unmet medical needs with regard to medicines for rare diseases and for children are covered by the parallel revision of the specialised legislations supported by its own impact assessment.[53]

The number of authorised medicines, both innovative and those with well-known active substances (e.g. generic and biosimilar medicines) is constantly on the rise. Since 2005, between 13 and 43 medicines with new active substances have been authorised in the EU every year, and 4-20 of those medicines address unmet medical needs[54]. However, there continue to be diseases with no or only few treatment options, e.g. neurodegenerative or infectious diseases. These unmet medical needs affect millions of EU citizens[55]. In the public consultation[56], all stakeholders found that the

[52] Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU, OJ L 458, 22.12.2021, p. 1.
[53] Cf. Ongoing Impact assessment for Medicines for children and rare diseases: https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12767-Medicines-for-children-rare-diseases-updated-rules_en
[54] Analytical report, indicator RI-9, Annex 10.
[55] The number of people living with dementia in the EU27 is estimated to be 7,853,705 and Alzheimer's disease is the most common form of dementia, Other dementias | Alzheimer Europe (alzheimer-europe.org).
[56] https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12963-Evaluation-and-revision-of-the-general-pharmaceutical-legislation/public-consultation_en.

legislation moderately promotes the development of medicines for unmet medical needs, with industry having the most positive view in that regard. While the general pharmaceutical legislation is not alone responsible for the problem of unmet medical needs[57], it can be instrumental in addressing some of the problem drivers within its remit.

AMR - a specific case of unmet medical need

An important area of unmet medical need is drug-resistant infections due to the emergence and spread of pathogens that have acquired new resistance mechanisms leading to AMR. AMR is responsible for an estimated 33 000 deaths per year in the EU and amounts to an estimated €1.5bn every year in healthcare costs and productivity losses[58]. At the same time the pipeline for novel antimicrobials that can fight resistant pathogens is very weak.[59] There is an apparent market failure and the lack of market incentives has led to underinvestment by big pharma companies in new compounds. Annex 15 further describes the market failure in this area.

Unequal access to medicines across the EU

The evaluation showed that the legislation has limited effect and relevance to ensure patient access to medicines. Access also depends on external factors[60] such as strategic decisions by companies whether and when to launch a product in a given Member State and national pricing and reimbursement policies. However, the general pharmaceutical legislation can have an impact on access through its incentives.

The number of authorised medicines in the EU has increased over time: 1 160 centrally authorised medicines (CAPs) were authorised in the period 2005-2020 and more than 17 000 medicines, primarily generic medicines, were authorised through mutual recognition and decentralised procedures in the same period[61]. However, patient access to medicines varies considerably across the EU[62]. The number of EU countries in which CAPs are launched has been steadily decreasing[63]. Substantial differences have been reported in terms of time to entry on the market[64].

Most medicines are – after authorisation – subject to national pricing and reimbursement decisions and, in particular for innovative and costly medicines, also HTA. The evidence requirements for these decisions (on relative/cost effectiveness of new medicines compared to existing treatments) are different than for the authorisation of those medicines, which is based on a positive benefit-risk balance for patients. Evidence required for HTA or pricing and reimbursement decisions are (often) not generated by companies by the time of the authorisation of the medicine and this may delay access. However, the recently adopted HTA Regulation intends to improve the situation, though its effects could not yet been taken into account in the evaluation and the consultations.

Evidence[65] shows that, whilst in Germany 133 out of 152 (i.e. 88%) new medicines authorised between 2016 and 2019 at EU level were accessible to patients, small Member States such as the Baltic Member States or Member States with comparatively low prices or with low GDP, like Romania, had fewer than 50 of these available[66]. The time to patient access is also significantly

[57] External factors (e.g. scientific barriers) are mentioned in the problem drivers for unmet medical need, see section 2.2.
[58] A European One Health Action Plan against Antimicrobial Resistance (AMR) (June 2017).
[59] Of 43 antibiotics in development, 15 were in Phase 1 clinical trials, 13 in Phase 2, 13 in Phase 3, and two have had new drug applications submitted. Historically, about 60% of drugs that enter Phase 3 will be approved.
[60] See Annex 14 on the factors influencing access to affordable medicines
[61] Analytical report, indicator ACC-1, Annex 10.
[62] Technopolis Evaluation study report, figure 10, 2022.
[63] Kyle, M.K, (2019). The Single Market in Pharmaceuticals. Review of Industrial Organization, 55(1),111-135. https://doi.org/10.1007/s11151-019-09694-6
[64] Bergmann et al., 2016, Ferrario (2016). Access to innovative oncology medicines in Europe. Annals of Oncology, 27(2), 353-356. https://doi.org/10.1093/ANNONC/MDV547
[65] Data from European Federation of Pharmaceutical Industries and Associations (EFPIA) and IQVIA.
[66] Newton et al. (2021). *EFPIA Patients W.A.I.T. Indicator 2020 Survey*.

longer for most of these latter countries, e.g. approximately two years or more after marketing authorisation in Romania compared to four months in Germany. Similar observations were made across different subsets of medicines. As a result, patients may not have had access to any appropriate treatment for their disease.

Although access depends, as explained above, on a multiplicity of factors, most respondents in the targeted survey, except industry agree that there is still room for improvement of the EU legislation in terms of access.

Most of the nationally authorised medicines are generic medicines[67]. Generic and biosimilar medicines can be marketed only after the expiry of regulatory and other intellectual property protection periods of the original medicine. They normally drive prices down and improve access. Low volume markets still experience limited access to generics.

Affordability of medicines is a challenge for health systems

Innovative medicines are often costly. Medicine prices vary significantly between Member States[68]. A study showed that list prices were the highest in Germany and the cheapest in many different EU countries but never in those with lower GDP like Bulgaria or Romania[69]. The medicines analysed were unaffordable for many EU health systems. Pharmaceutical budgets also put pressure on health systems. Medicines in hospitals account for over 20-30% of hospital expenditures and are growing[70].

In 2013-2019, the average household out-of-pocket (including regulated co-payments) share of non-hospital medicines is stable, at around 28-30%, but there are big differences between the MS with countries like Germany and France having shares below 20% and Poland and Bulgaria over respectively 60 and 70%.[71] Out-of-pocket payment for medicines is outside of the remit of the pharmaceutical legislation. Other external factors are described in Annex 14.

Against this backdrop, generic and biosimilar entry can be an important factor in terms of competition, to achieve lower prices, broadening patients' access and alleviating healthcare costs[72]. In the EU, the share of generics in total medicines sales revenue modestly increased (from 13% to 16%) between 2002-2020[73]. An analysis shows that the EU is on a similar trend as other comparable markets (Japan and USA)[74]. Nonetheless, inquiries show that originator companies sometimes use various practices (such as "evergreening" or "killer acquisitions" early in the pipeline) to delay or prevent generic/biosimilar entry. These anti-competitive practices can be prosecuted by EU competition authorities. The evaluation confirms that further efforts can be made to fully exploit the savings generated by the generic and biosimilar competition; although measures in this regard are primarily outside the scope of the general pharmaceutical legislation, the revision can improve the conditions for generic and biosimilar authorisation and competition.

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[67] Study on the experience acquired as a result of the procedures for authorisation and monitoring of medicinal products for human use, EY, January 2020, p. 103.

[68] The desk research suggests for example an almost 11-fold difference between interferone-beta list prices in Germany (€1451.17) and Croatia (€132.77); list prices do not include the confidential rebates (if they exist) or 'price freezes' and may therefore not correspond to the actual price.

[69] Zaprutko T, Kopciuch D, Kus K, et al. Affordability of medicines in the European Union. *PLoS One*. 2017;12(2):e0172753.

[70] European Commission, State of health in the EU: companion report 2019 (ISBN 978-92-76-10194-9)

[71] OECD, Eurostat and World Health Organization (2017), A System of Health Accounts 2011: Revised edition, OECD Publishing, Paris. http://dx.doi.org/10.1787/9789264270985-en).

[72] IMS Health (2015) The Role of Generic Medicines in Sustaining Healthcare Systems: A European Perspective

[73] Evaluation SWD, section 4.1.1.4, Annex 5.

[74] Ibid, footnote 67.

The probability of competition is lower for (a) biosimilars than for generics; (b) products with manufacturing complexity and (c) products with smaller turnover (e.g. for rare diseases).[7576]

According to all stakeholder groups, enabling access to affordable medicines is among the areas where the legislation has been less effective. The rising costs of medicines were key concerns for academics, healthcare professionals, public authorities and civil society stakeholders.

Shortages of medicines

The evaluation showed that medicine shortages are an increasing problem in the EU; a problem that was also experienced during the COVID-19 pandemic. Over the last 10 years, there has been a strong increase in the number of shortages notified in the EU from a few in 2008 to nearly 14 000 in 2019[77]. There are a number of root causes. These include: more complex and diversified global supply chains, quality and manufacturing challenges and commercial decisions or unexpected increase in demand. Evidence shows that medicine shortages are placing a significant burden on health systems, health professionals and are ultimately putting patients at risk of sub-optimal care and health systems at risk of higher healthcare costs[78].

Medicine shortages have also a global dimension due to the global supply chain, where external actions or events impact the supply of medicines in the EU, e.g. the Indian export restriction of certain active substances during the COVID-19 pandemic. Likewise, problems at a manufacturing site may cause shortages in several Member States or the whole EU, depending on the supply chain.

The public consultation confirms the importance all stakeholders (in particular civil society organisations and healthcare professionals) place on medicine shortages. In the targeted survey, civil society, public authorities and health service stakeholders considered that the legislation is the least effective in addressing issues related to security of supply and medicine shortages.

The general pharmaceutical legislation can provide harmonised tools to allow Member States to better handle medicine shortages and thus act as enabler for addressing the problem.

The regulatory system does not sufficiently cater for innovation/unnecessary administrative burden

While the system for authorisation and monitoring of medicines in the EU overall meets the objectives of the general pharmaceutical legislation, rapid scientific and technological developments have resulted in new challenges for the system, which has become more complex over time, as reflected by the expansion of the number of EMA scientific committees and their interactions[79]. New types of medicines (e.g. personalised medicines), approaches and processes, may raise questions about whether they fully fit within the scope of the legislation and can find themselves subject to unintended barriers to innovation, development, production or marketing authorisation. Products combining medicines with technologies regulated under other frameworks (e.g. medical devices, artificial intelligence) or products using new platform technologies[80] face uncertainty about the applicable framework. Likewise, the current framework is not adapted to novel production technologies or methods (e.g. decentralised manufacturing). Borderline issues for ATMPs with the BTC framework, which provides starting materials, were also highlighted in the evaluation.

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[75] SWD(2020) 163 final, p. 58.
[76] Understanding Net Pharmaceutical Expenditure Dynamics in Europe, April 2022, IQVIA.
[77] Analytical report, indicator SM-1, Annex 10. Data only collected for period 2008-2020, during which many Member States put in place new systems or requirements for notification of shortages.
[78] European Commission, Directorate-General for Health and Food Safety, Jongh, T., Becker, D., Boulestreau, M., et al., Future-proofing pharmaceutical legislation: study on medicine shortages: final report (revised), 2021, https://data.europa.eu/doi/10.2875/211485.
[79] COM(2021) 497 final.
[80] When a certain process/method is used to manufacture specific individualised treatments, i.e. adjustments to the medicine are made based on the characteristics of the patient or the causing pathogen.

The consultations showed a consensus between academia/research organisations, patient/consumer organisations, healthcare professionals and industry that the legislation was not flexible enough to accommodate scientific advances, such as real-world data in healthcare. Public authorities noted that medicines regulators need more resources to keep up with the speed of scientific and technological developments and to assess complex therapies appropriately.

Digital transformation has been changing the health sector. However, there is an overall lack of transparency and interoperability; digital expertise and infrastructure are not sufficiently available across the Member States and the EU regulatory network. All stakeholders agreed that EU telematics systems play an important role in contributing to the efficiency of the system, but also identified room for improvement (like a very complex governance system for EU telematics).

An assessment of the current authorisation system[81] identified the need for rationalisation and simplification which the consultations echoed. Stakeholders noted the need for strengthened coordination between bodies responsible for marketing authorisation procedures, clinical trial authorisations, HTA and pricing and reimbursement. Several industry respondents stated that regulatory burden can be costly, duplicative and thus hinder innovation, in particular for innovative SMEs who may struggle with high fee costs, though fees incentives exist for SMEs[82].

Medicines in the environment

While the positive effect of medicine for treatment of diseases is undisputed, pollution caused by medicines is a well-documented risk to the environment and human health, particularly in relation to antimicrobial resistance. Residues of medicines may enter the environment during their manufacturing, use by patients and disposal, with the largest source being the use[83]. Residues of medicines have been found in surface and ground waters, soils and animal tissues across the EU at concentrations depending on the medicine and the proximity of sources[84]. Traces have also been found in drinking water. Residues of medicines in the environment is a global problem[85]. The evaluation confirmed that the current requirement for an environmental risk assessment (ERA) before marketing authorisation has some weaknesses as regards compliance, content and scope.

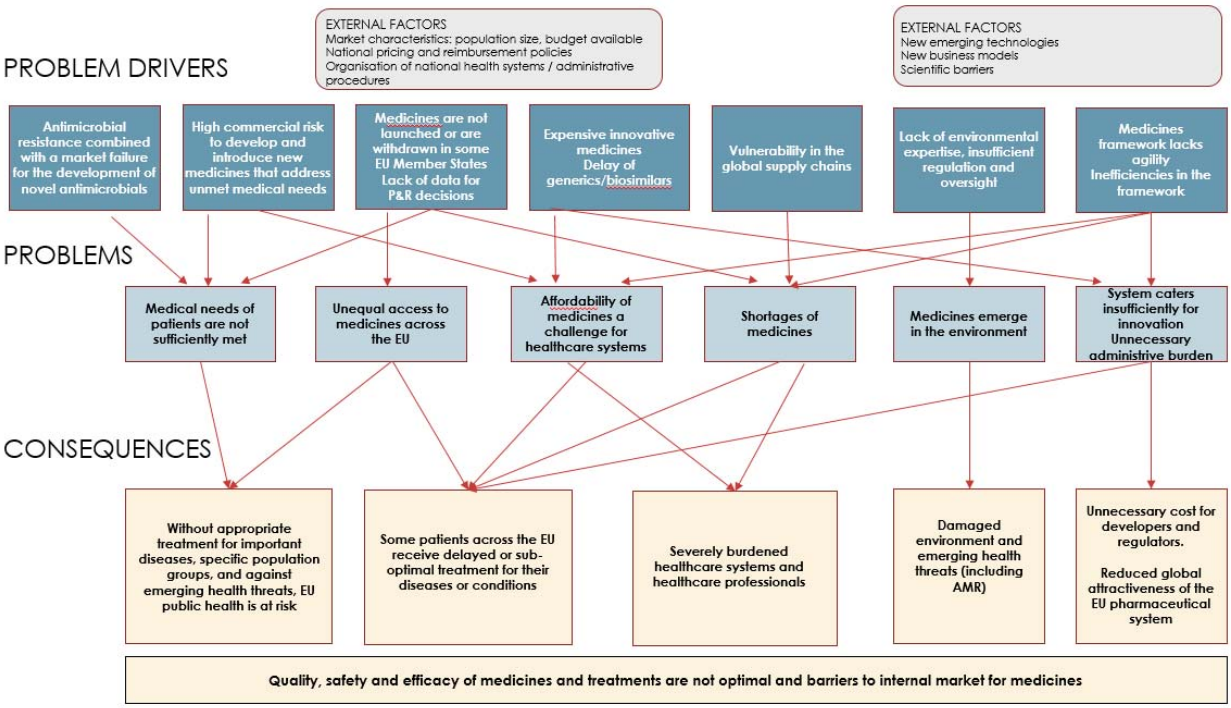
In the targeted consultations, the stakeholders (industry, civil society and public authorities) ranked reducing the environmental impact of medicines among the objectives where the general pharmaceutical legislation had been the least effective. In the public consultation, the stakeholders across the board found that the legislation has performed moderately in ensuring that medicines are manufactured, used and disposed of in an environmentally friendly manner, with citizens, healthcare professionals and public authorities being the most critical.

2.2 What are the problem drivers?

Figure 1 provides an overview of the problem drivers and their link with the problems identified.

[81] COM(2021) 497 final.
[82] Commission Regulation (EC) No 2049/2005 provides for specific support for SMEs, including an SME Office in the EMA and fee reductions and deferrals. Further fee incentives for SMEs are provided in the Rules for implementation of the two fee regulations (Council Regulation (EC) No 297/95 and Regulation (EU) No 658/2014).
[83] COM(2019) 128 final.
[84] Analytical report, indicator E-1, Annex 10.
[85] Idem.

Figure 1 Problem tree diagram for the revision of the general pharmaceutical legislation



The problem drivers that are causing underperformance on the ground are a series of complex, interlinked factors.

Drivers for unmet medical needs

Despite the fast-paced advances in science and technology, scientific barriers prevent the development of medicines to treat or cure some diseases such as Alzheimer's. For unmet needs, there are a series of different drivers, e.g. market failure, complexity of disease pathologies, knowledge gaps in molecular and physiological underpinnings of diseases, high risk R&D. While the EU has a world-leading, research-intensive pharmaceutical industry[86], evidence suggests that R&D costs per new medicine have increased over time with estimates ranging from US$944m to US$2,826m with great variability across therapeutic fields[87]. This is one among the drivers that have increased the commercial risk of developing new medicines for **unmet medical need**.

Big pharma companies tend to disinvest from riskier upstream research and to choose R&D investments that will maximise their future profits through licensing or acquisitions of products that are already in later clinical trial stages with good probability for marketing authorisation, sales and high price.[88] Such business strategies are not always aligned with the public goal of directing efforts towards the greatest unmet medical needs. Furthermore, the pharmaceutical legislation makes no distinction in regulatory incentives granted to highly innovative medicines addressing unmet medical need and those for incremental innovation, such as 'me-too' medicines (similar to existing medicines) without added therapeutic value. This gives less incentive to invest in higher risk development of the former. There is a concentration of investment in areas where there is less

[86] The Pharmaceutical Industry in Figures, Key Data 2021 (EFPIA, 2021).
[87] Simoens, S., & Huys, I. (2021). R&D costs of new medicines: a landscape analysis. *Frontiers in medicine*, *8*, available at https://www.frontiersin.org/articles/10.3389/fmed.2021.760762/full.
[88] EPRS_STU(2021)697197_EN.pdf (europa.eu): European pharmaceutical research and development. Could public infrastructure overcome market failures?

financial risk, e.g. oncology. When companies invest in less risky areas, even incremental innovation can lead to an economically viable or profitable product.

The **growing resistance of pathogens to antimicrobials (AMR)** combined with the weak global pipeline of major new classes of antimicrobials are a special driver for unmet medical need. A growing market failure derives from the fact that the typical cost of surpassing the scientific challenges involved in developing new antimicrobials is very high and at the same time the typical income and profit that can be derived from sales of these products are very limited because healthcare systems want to keep new antimicrobials in reserve or limit their use so as not to fuel the vicious cycle of AMR, by inappropriate use of already authorised antimicrobials.

Drivers for access to medicines

A key **access problem driver** is that authorised **medicines are not launched in all Member States or are subsequently withdrawn**. Currently, companies have the choice where and when to launch centrally authorised medicines, the legislation only requires them to place their product on the market in at least one Member State within three years of its authorisation (the so-called 'sunset clause'). Other than that, companies have a free hand; this creates an unpredictable situation for patients and Member States. With some Member States companies enter into pricing and reimbursement negotiations only very long time after marketing authorisation or not at all. The decision for the company to launch and when depends on different factors for example the size of the patient population, or national pricing and reimbursement policies, and the organisation of health systems. These factors influence whether the company can successfully pass a HTA in that Member State and finally negotiate a price and a reimbursement status for the product.

Access may also differ due to organisational differences in Member States (different medical protocols, access to specific equipment/infrastructure needed for administration, different characteristics of the health systems).

The pharmaceutical legislation has no direct influence on HTA and pricing and reimbursement processes or the organisation of the national health systems. However, the general pharmaceutical legislation and its system of regulatory incentives can be an enabling factor to improved access by incentivising market launch by companies, strengthening the position of national pricing and reimbursement bodies, facilitating collaboration among decision makers along the lifecycle of a medicine and by increasing competition from generics and biosimilars.

For a more detailed analysis on the factors and dynamics behind the market launch, the access chain, HTA, pricing/reimbursement process and on pharmaceutical expenditure please refer to Annex 14.

Withdrawals of medicines disrupt the established access chain (from authorisation to entry into the health system). An available product abruptly or gradually withdrawn from the market (often for commercial reasons) can create **shortages** and leave patients without treatments.

Drivers for affordability of medicines

Pharmaceutical expenditure is largely subsidised by national health systems in order to ensure the adequate provision of medicines to all their respective citizens. New, highly **innovative medicines** may place pressure on public budgets due to their prices. Therefore, Member States adopt measures to regulate the prices of medicines and the conditions of their public funding based on their exclusive competence in this field (Article 168 TFEU). Member States follow different **price and reimbursement policies** and the pharmaceutical markets remain very fragmented by country (for a review of pricing policies[89]). The External Reference Pricing (ERP) policy, for which the price set for the same product in one or several countries is used as a benchmark for setting the product's price in a given country, is the most frequently used pricing policy in Europe. As a consequence of

[89] WHO guideline on country pharmaceutical pricing policies, Geneva: World Health Organization; 2020.

differences in prices, the use of ERP and parallel import, and differences in market size, the availability and entry date of medicines strongly differ among Member States.

The prices by country do not depend only on the government regulation (such as price controls and reimbursement decisions) but also on several other factors, such as income per capita, the size of the market, the characteristics of the product (innovative or old, its therapeutic advantages etc.), the patent status, the presence of competitors and research costs incurred (also for unsuccessful development of medicine)[90]. However, there is a lack of transparency on R&D costs or public contributions to these costs. While R&D costs are not relevant for the assessment of a medicine's benefit-risk balance, information on such costs are relevant for the downstream actors and may facilitate their decision-making.

Delay in generic and biosimilar entry is also a driver for expensive innovative medicines.

The general pharmaceutical legislation has only an indirect impact on the affordability of medicines by facilitating competition and early market entry by generic and biosimilar medicines. In a similar way, it streamlines procedures and makes the regulatory framework more efficient thereby lowering costs for authorisation or manufacturing which could have an impact on the price of the medicine.

Drivers for shortages of medicines

Vulnerability in the global supply chains has arisen from global industry consolidation with increased complexity in supply chains, in which many different intermediate suppliers may be connected, and, in particular for generic medicines, from reliance on a few, specialised overseas suppliers that produce at lower prices. In addition, the notification and obligation to ensure appropriate and continued supply, varies across Member States with e.g. 4 months in advance notification of shortages in Italy and at least 6 months in Romania[91].

While Member States have already introduced a variety of actions at the national level to help protect their security of supply, the impact of these measures on preventing and mitigating the impact of shortages is not yet sufficiently understood.

Drivers for medicines into the environment

The **lack of relevant or insufficient regulation and oversight** currently influences the effects medicines use may cause for the environment, while a lack of environmental expertise influences the understanding of the effects on the environment from medicines. The largest source of medicines entering the environment is the use of medicines; due to the chemical and/or metabolic stability of some medicines, as much as 90% of the active substance is excreted or washed off into the environment in its original form[92]. Pharmaceuticals mainly reach the environment through:

- the discharge of effluent from urban waste water (sewage) treatment plants – containing excreted pharmaceuticals as well as unused pharmaceuticals thrown away into sinks and toilets, despite the existence of collection schemes;
- the spreading of animal manure; and
- aquaculture, in which pharmaceuticals are often dispensed with the animal feed.[93]

Another source is the discharge of effluent from manufacturing plants (especially those outside the Union) with potential impacts that may significantly effect on a local scale when manufacturing

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[90] Zaprutko T, Kopciuch D, Kus K, et al. Affordability of medicines in the European Union. *PLoS One*. 2017;12(2):e0172753.
[91] European Commission, Directorate-General for Health and Food Safety, *Future-proofing pharmaceutical legislation: study on medicine shortages: final report (revised)*, 2021, https://data.europa.eu/doi/10.2875/211485.
[92] COM(2019) 128 final.
[93] Idem as 92.

emissions of wastewater are inadequately managed.[94] Environmental legislation, such as the Urban Waste Water Directive – currently under revision – and other environmental legislation and initiatives mentioned in section 1.1, is the main instrument for addressing reduction of medicines residues and hence the environmental impact of the industry; however, not even the best and most expensive current wastewater treatments are 100% effective. The measures in this revision complement environmental legislation.

Drivers for lack of innovation and inflexible regulatory framework

The rapid pace of the scientific and technological development is a driver for – and an external factor to – the problem that the regulatory system does **not sufficiently cater for innovation**. The general pharmaceutical legislation is often prescriptive, and it takes a long time to amend it. Hence, the **medicines framework lacks agility** to respond to rapid developments.

Inefficiencies in the regulatory framework were identified in the evaluation, e.g. redundant requirements like the 5-year renewal of marketing authorisation, leading to unnecessary administrative burden. In addition, there is duplication of assessment by the medicines authorities, for instance when different companies apply for authorisation of the same product with the same clinical trial in different procedures. There is insufficient pan-European digital infrastructure and legal basis for optimal use of electronic tools for companies or medicine authorities which contributes to a loss of competitiveness. Better use of digitalisation in the framework, e.g. through electronic product information, could help combat shortages, increase access in smaller markets and also support competition, while improving information on medicines.

2.3 How likely is the problem to persist?

If no EU action is taken, the problems described will persist. While more medicines are expected to be authorised (for CAPs this might increase to 40-60 medicines containing new active substances per year[95]), these medicines will not necessarily address unmet medical needs to a greater extent than today. For example, recently approved antibiotics[96] and the clinical pipeline are insufficient to tackle the increasing emergence and spread of antimicrobial resistance[97]. The market failures in this area will not be corrected without interventions on several fronts, including the general pharmaceutical legislation. The persistence of the problems is also confirmed by some of the megatrends identified by the EU Joint Research Centre[98]. The megatrend on shifting health challenges describes demographic changes and environmental challenges that could create new unmet medical needs and public health burdens as demonstrated by the COVID-19 pandemic.

Authorised medicines will continue to be inaccessible at affordable prices in some Member States. The 'access chain' mechanism mentioned above and analysed in Annex 14 is affected by deficiencies that are systemic in nature and some of the 'links' lie outside the remit of this legislation. Nevertheless, the analysis of the policy options in section 6 shows that the revision of the legislation can act as a key enabler for access and can influence affordability. The policy interventions in the legislation shall be complemented by other actions of the pharmaceutical strategy, e.g. best practice exchange between Member States on pricing, payment and procurement.

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[94] Larsson DGJ. 2014 Pollution from drug manufacturing: review and perspectives. *Phil. Trans. R. Soc* ***369****:20130571*.
[95] Described in section 5.1.1.
[96] Since 2015. 11 antibacterials with new active substance have been granted a Union marketing authorisation, though none of these products constituted a new class of antibiotic.
[97] Antimicrobial products in clinical development for priority pathogens (April, 2021), 68 products are in development (41 antibiotics and 27 non-traditional antibacterial agents) see https://www.who.int/observatories/global-observatory-on-health-research-and-development/monitoring/antibacterial-products-in-clinical-development-for-priority-pathogens.
[98] The Megatrends Hub | Knowledge for policy (europa.eu)

Since new scientific and technological developments will continue, some problems may exacerbate if the legislation is not future-proof. Current work-arounds which are based on 'creative' interpretation will become bottlenecks, especially for complex products. Borderlines between product categories may be more blurred and determination of applicable legal frameworks and their interaction may become complex, leading to longer development or authorisation processes for innovative medicines and thus a longer time to reach patients. This impacts negatively innovation while some innovative products may remain unregulated with negative effect on public health.

If the efficiency of the regulatory system will not be improved and administrative burden not reduced, e.g. by digitisation, valuable resources might not be available to facilitate the development and the assessment of innovative medicines. Likewise, resources might not be available to invest in the expertise needed to cope with new scientific and technological developments. For the industry, there might be less investment in new medicines and hence fewer new medicines authorised, reduced innovative capacity and competitiveness. The megatrend on accelerating technological change and hyperconnectivity is particularly relevant both in terms of development and innovation of medicines and of digitisation of the regulatory system.

Likewise, the problem of medicine residues in the environment will persist if no EU action is taken with risks to flora, fauna and habitat due to the pharmacological characteristics of the active substances. The megatrend on increasing demographic imbalances with the ageing population in the EU may exacerbate the environmental challenges from medicines as elderly people tend to use more medicines than young people; this could also put further pressure on national health systems.

3 WHY SHOULD THE EU ACT?

3.1 Legal basis

The general pharmaceutical legislation is based on Articles 114 and 168 of the Treaty on the Functioning of the European Union (TFEU). These articles provide the legal basis for the EU to adopt measures which have as their object the establishment and functioning of the internal market (Article 114(1)) as well as setting high standards of quality and safety of medicinal products (Article 168(4)(c)). While the internal market and common safety concerns in public health matters fall within a shared competence of the EU and Member States, once the EU adopts harmonised legislation in such an area, Member States can no longer exercise their own competence. This is the case for the general pharmaceutical legislation. Any future legislative proposals, supported by this impact assessment, will be based on Articles 114(1) and 168(4)(c) TFEU. It will also consider Article 35 of the EU Charter of Fundamental Rights that provides that the Union is to ensure a high level of human health protection in the definition and implementation of Union policies.

As per Article 168(7) of the TFEU, Member States are responsible for the definition of their health policy and for the organisation and delivery of health services. Consequently, coverage and pricing decisions for medicines are outside the scope of the legislation.

3.2 Subsidiarity: Necessity of EU action

Diseases do not know borders. Common provisions for the authorisation of medicines constitute a cross-border issue for public health that affects all Member States and thus can effectively be regulated only at EU level, given that the authorisation of medicines is fully harmonised at EU level.

The objectives this revision intends to achieve benefit all Member States. EU action relies also on the single market to achieve a stronger impact as regards access to safe, effective and affordable medicines, as well as the security of supply across the EU. National actions are likely to create disharmonised solutions resulting in fragmentation, and possibly exacerbate some of the problems to be solved, distort competition and increase administrative burden for the pharmaceutical companies, which often operate in more than one Member State. An example of fragmentation is the additional

and non-harmonised measures introduced by Member States to prevent and mitigate medicines shortages[99]. A harmonised approach at EU level also provides greater potential for incentives to support innovation and for concerted action for development of medicines in areas of unmet needs.

The legislation respects Member States' exclusive competence in the provision of health services, including pricing and reimbursement policies and decisions. In this respect, the Pharmaceutical Strategy provides for supporting non-legislative actions such as cooperation mechanisms, e.g. through a group of competent authorities, based on mutual learning and best practice exchange on pricing, payment and procurement policies. These exchanges can be facilitated at EU level.

3.3 Subsidiarity: Added value of EU action

This initiative revises a system with recognised EU added value for the EU patients/citizens, pharmaceutical industry and medicines authorities through e.g. timely authorisation, patient access and continuous supply of innovative and established medicines and strong cooperation[100].

This revision is expected to bring further benefits by addressing unmet medical needs and contributing to reducing the unequal patient access to medicines across the EU. At the same time, simplification and streamlining of processes are expected to reduce administrative burden for companies and authorities and hence improve efficiency and attractiveness of the EU system.

This revision can influence positively the competitive functioning of the market through the review of the incentives and other measures to facilitate early entry on the market of generic and biosimilar medicines and hence improve patient access and affordability.

These benefits and cost-savings can best be achieved by EU action, while recognising that external factors such as national pricing and reimbursement policies and company decisions to launch medicines have great impact on patients' access to medicines. Furthermore, science and technological developments, as well as R&D policies and company investment decisions influence innovation, especially for unmet medical needs.

The measures to support security of supply under this initiative relate to the responsibilities of marketing authorisation holders and supply chain actors like wholesalers. Those actors are already covered by the EU pharmaceutical legislation. However, measures supporting security of supply go beyond legislative measures; many actions do actually take place already at national level and will continue to do so. National and EU levels are not alternatives to each other, but complementary.

In a few instances, the evaluation identified problems with a harmonised implementation of the Directive across Member States[101]. However, these problems relate to vague legal wording of the respective provision rather than the legal instrument used. Moreover, in 2019, a REFIT Platform Opinion[102] considered a suggestion to turn the Directive into a Regulation, though that suggestion did not receive overall support. The opinion showed that many Member States considered the system sufficiently harmonised and would not see a need for a Regulation.

4 OBJECTIVES: WHAT IS TO BE ACHIEVED?

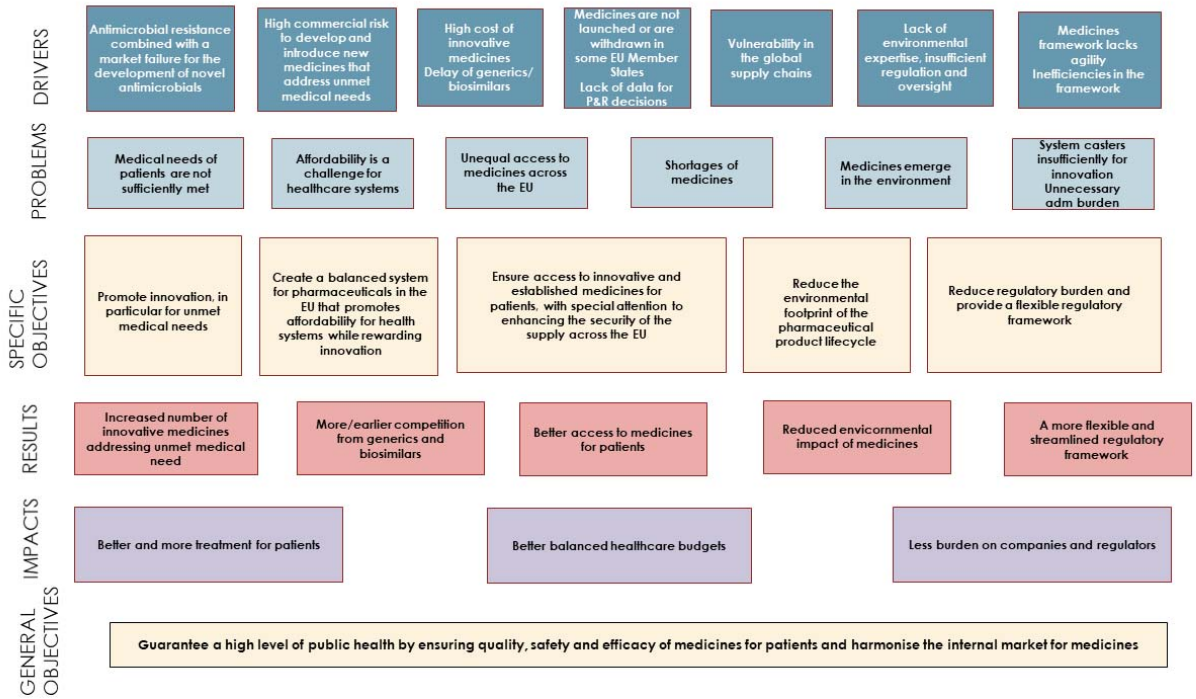
4.1 Introduction

This section sets out the general and specific objectives as well as the logic (Figure 2) underpinning the revision. It addresses the problems identified, and provides a focus for assessing and comparing

[99] European Commission, Directorate-General for Health and Food Safety, Future-proofing pharmaceutical legislation : study on medicine shortages : final report (revised), 2021, https://data.europa.eu/doi/10.2875/211485
[100] Evaluation SWD, section 4.2, see Annex 5.
[101] E.g. application of the Bolar provision – see page 7 of the evaluation SWD
[102] https://wayback.archive-it.org/12090/20200308120955/https:/ec.europa.eu/info/sites/info/files/xi.9.a_medicinal_products_for_human_use.pdf

the likely cost-effectiveness of the selected policy options. The two legislations constituting the general legislation make up a single intervention logic in this policy area.

Figure 2 Intervention logic for the general and specific objectives, problem drivers and problems



4.2 General objectives

The general objectives of the revision remain unchanged in that the general pharmaceutical legislation aims to 'guarantee a high level of public health by ensuring the quality, safety and efficacy of medicines for EU patients' and harmonise the internal market.

4.3 Specific objectives

In response to the problems identified, this revision aims to:

1. **Promote innovation, in particular for unmet medical needs**

The objective is to promote innovation with special focus on medical conditions not yet addressed and which represent a significant EU health burden (unmet medical needs). The revision should enable major biomedical research advances and ensure a pipeline of innovative new medicines for use across the EU. It should also support pharmaceutical R&D and strengthen the competitiveness of the research-based EU pharmaceutical sector.

The objective is also to address the market failure related to the development of novel antimicrobials through novel incentives that can finance the research required while respecting the need for a as limited as possible use of antimicrobials to reduce the tendency of pathogens to develop resistance.

2. **Create a balanced system for pharmaceuticals in the EU that promotes affordability for health systems while rewarding innovation**

This objective aims to enable competition, to promote affordability of medicines for health systems across the EU and ensure healthcare costs are sustainable for Member States. Affordability should not though be promoted at the expense of innovation, which also benefits patients. Thus, the underlying ambition is to create a balance where, on the one hand, innovation is rewarded, and on the other hand, faster market entry of generic and biosimilar medicines is facilitated, as a means to

improve competition across the EU. This is expected to drive down costs for medicines with the additional benefit of strengthening the EU generic and biosimilar industry.

Affordability is a new objective of the revision, which can only indirectly be impacted by the general pharmaceutical legislation.

3. Ensure access to innovative and established medicines for patients, with special attention to enhancing security of the supply across the EU

This objective aims to promote equal access to medicines for all EU citizens, including in smaller Member States, after a timely authorisation under the EU pharmaceutical system. After a medicine has been developed and become available after a timely authorisation under the EU pharmaceutical system, patient access has two dimensions: (i) equal access to/market entry of innovative medicines across the EU and (ii) continuous supply and limited shortages of all medicines. As regards the first, the aim is to provide a motivation to companies to rapidly reach an agreement with Member States and engage Member States in effective negotiations. Facilitating competition from generic and biosimilars will also serve the same objective. As regards the second dimension (shortages and keeping products on the market), the aim is to enhance and harmonise notification requirements and obligations to ensure appropriate and continued supply across Member States.

4. Reduce the environmental impact of the pharmaceutical product lifecycle

This objective aims to reduce the environmental impact of pharmaceuticals through minimising medicine residues in the environment from their production, use, and disposal. This would entail an enhanced assessment of environmental risks of medicines and appropriate risk mitigation measures, including on their prudent use, especially for AMR.

5. Reduce the regulatory burden and provide a flexible regulatory framework

This objective aims to create a more flexible regulatory framework, to future-proof innovation and reduce regulatory burden. Through simplifying and integrating regulatory requirements and pathways and reducing burden for industry and public authorities alike, this objective aims to increase the attractiveness of the EU regulatory system. The goal is to provide clarity on the appropriate regulatory pathway, reduce approval times and costs while maintaining high standards and robust assessment of the quality, safety, and efficacy of medicines. Leveraging digital technology and the use of electronic product information could support this objective.

Objectives 1, 2 and 5 work in synergy for promoting innovation as do objectives 2, 3 and 5, with a range of measures to achieve access to affordable medicines. Trade-offs have to be considered between objectives 4 and 5 as measures to reduce the medicine residues in the environment are likely to increase the administrative burden. Trade-offs have also to be carefully considered for measures under objective 3 to address the risk of shortages while reducing regulatory burden. Trade-offs between achieving access (objective 3) through possible costs of additional market launches and affordability (objective 2) may also be necessary. Trade-offs are also inherent in objective 2 between rewarding innovative medicines and affordability often achieved by generic/biosimilar competition.

The specific objectives are consistent with the European Green Deal and Digital agenda principles and with the right of access to preventive health care and the right to benefit from medical treatment set out in the EU Charter of fundamental rights[103]. In particular objectives 1 and 3 on innovation including for unmet medical needs and on access to medicines will have a positive effect on the access of patients to the medicines they need which relates to Article 35 of the Charter of fundamental rights of the EU which establishes the right to benefit from medical treatment under the conditions established by national laws and practices and a high level of human health protection in

[103] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A12012P%2FTXT

the definition and implementation of all the Union's policies and activities. Objective 4 which is expected to reduce medicines' residues in the environment from their manufacturing, use and disposal is in line with the objectives set out by Article 37 on environmental protection.

5 WHAT ARE THE AVAILABLE POLICY OPTIONS?

5.1 What is the baseline from which options are assessed?

The baseline is represented by the business-as-usual scenario, that is, the situation where no policy changes are made.

The current system provides 8 years of data protection and 2 years of market protection for all innovative medicines, to give time to developers to recoup their investment by delaying the entry of generic or biosimilar medicines. Other incentives also exist in parallel that delay generic/biosimilar competition (patent, SPC, orphan market exclusivity, paediatric protection extensions), usually offering a longer than 10-year protection if a medicine is eligible. However, the regulatory data and market protection is the broadest in terms of eligibility, as it applies to all innovative medicines, and it is almost impossible to infringe it[104].

The current legislation also provides an additional 1 year regulatory protection for a new indication with significant clinical benefit, allowing thus a maximum of 11-year protection. The revision does not consider changing this incentive. Therefore, this incentive is not presented in the options.

Currently, there are no special incentives or obligations for the development of new antimicrobials or prudent use of existing ones, nor for conducting comparative clinical trials.

There are no incentives or obligations on MAHs to place their products on the markets that do not offer a sufficient business case. In essence, even when receiving an EU-wide marketing authorisation, a company is completely free to choose where and when it will market its product. There is no predictability for Member States who have no way of obliging the company to initiate negotiations for pricing and reimbursement. The steps from a medicine's marketing authorisation to access and the influencing factors are described in Annex 14. There is no requirement for MAHs to be transparent about public contribution to R&D costs either.

With regard to shortages, the current system focuses on notifying supply disruptions; it obliges MAHs to notify competent authorities 2 months in advance if they expect a temporary or permanent withdrawal of a medicine. Moreover, MAHs and wholesalers have to ensure appropriate and continued supplies of medicines, however without effective means to enforce the obligations.

The ERA is the main mechanism within the current legislation for addressing environmental impact of pharmaceuticals. It is required for all new MA applications and covers the environmental risks of the use, storage and disposal of pharmaceuticals. It does not include environmental effects of manufacturing. While it provides data to assess the impact of medicine residues released into the environment, there are gaps in timely enforcement and possible risk minimisation measures.

SMEs have a fundamental role in the development of medicines. According to a recent report from IQVIA[105], emerging biopharma companies (defined differently than SMEs in the EU, but essentially the same category) were responsible for a record 65% of the molecules in the R&D pipeline in 2021, up from less than 50% in 2016 and 33% in 2001. The trend is that small companies dominate the earlier development stages, which are not too expensive but very risky. Once the molecule reaches a

[104] Before authorising a generic/biosimilar product, national competent authorities check against the data protection or market exclusivity of the reference medicine and do only authorise the generic if these protections have expired.
[105] 'Global Trends in R&D: overview through 2021,' IQVIA Institute for Human Data Science, February 2022.

certain maturity and still looks commercially promising, the SME typically partners[106] with big pharma companies, which come in at the stage of the expensive late-stage clinical trials, marketing authorisation and market launch that often require vast capital and global infrastructure.

5.1.1 Projections

The life sciences sectors continue to invest in and advance innovative therapeutics and vaccines, the total number of products that are in active development globally exceeds 6 000, up 68% over the 2016 level.[107] Rich pipelines translate to more medicine authorisations, and we assume that the current annual 30-40 authorisations of medicines with new active substances in the EU will expand to 50-60 in the next 15 years. In our **dynamic baseline**, we will take the middle value at the middle of the next 15-year period, **45 innovative medicines per year** to analyse the impacts of the various policy measures proposed.

Against the backdrop of the overall positive outlook for innovation, research efficiency declines and it costs more money and requires more failures to develop a new medicine[108]. Investments in R&D are driven by commercial interest rather than public health needs, leaving important unmet medical needs unaddressed. We expect that **15-20%** of the new innovative medicines, or **7-9 medicines per year will address a real unmet medical need** without changes to the baseline, based on the current ratio of accelerated assessments at the EMA[109].

According to WHO, drug-resistant bacterial diseases already cause at least 700 000 deaths globally a year, including 230 000 deaths from multidrug-resistant tuberculosis, a figure that could increase to 10 million deaths globally per year by 2050 under the most alarming scenario if no action is taken and no new antibiotics are developed and authorised.

Regarding access to medicines, a IQVIA survey[110] shows no major improvement over the last year, with a **90% variance** between Northern and Western European countries and Southern and Eastern European countries **in terms of patient access to new medicines**, which also largely **corresponds** to the launch patterns according **to market size and purchasing powers** described in section 2.1 and Annex 14 due to pricing and reimbursement policies. The average delay between market authorisation and patient access can vary by as much as a factor of seven across EU, from as little as 4 months to 29 months. Maintaining the baseline would likely conserve the problem at today's level.

Available evidence suggests that across the EU the frequency of shortages and their impact on patients and healthcare providers is increasing[111].

If no changes are made to current requirements, the effect of the ERA to manage environmental risks would remain limited. The main effect to reduce medicines in the environment should come from environmental legislation.

5.2 Description of the policy options

In order to respond to the specific objectives, we considered more than 70 potential policy measures deriving from the consultation process and initial analysis. These measures were organised around nine policy blocks reflecting the objectives of the revision and its broad scope[112].

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[106] Big pharma may acquire the rights for the product, the whole company, or they develop, authorise and market the medicine in a joint partnership (e.g. the Pfizer-BioNTech COVID-19 vaccine).
[107] 'Global Trends in R&D: overview through 2021,' IQVIA Institute for Human Data Science, February 2022.
[108] idem
[109] Annex 5 – Evaluation SWD, p.22
[110] EFPIA Patients WAIT Indicator 2021, see: https://www.efpia.eu/media/636821/efpia-patients-wait-indicator-final.pdf
[111] European Commission, Directorate-General for Health and Food Safety, Future-proofing pharmaceutical legislation : study on medicine shortages : final report (revised), 2021, https://data.europa.eu/doi/10.2875/211485

In a second step, taking into account the preliminary evaluation findings, we designed the three high-level options which represent alternative ways to reach all the objectives of the revision. Each option is constructed around specific underlying principles behind the grouping:

- Option A builds on status quo and achieves the objectives mainly through new incentives;
- Option B reaches the objectives through more obligations and oversight;
- Option C adopts a 'quid pro quo' approach in the sense that positive behaviour is rewarded and obligations are only used when there are no alternatives.

Each option contains pivotal and non-pivotal measures. Non-pivotal measures are complementary to the pivotal ones and form an integral part of the policy options. A thorough multi-criteria impact analysis for each policy measure, based on data, literature review and stakeholder feedback can be found in Annex 11.[113] Finally, the options are complemented by horizontal measures. Contrary to the non-pivotal measures, they apply across the board and deliver on simplification and innovation.

The IA report focuses on the 'pivotal' measures and the 'pivotal horizontal measures'. These pivotal measures were selected on the basis of the magnitude of their impacts and their political importance. **Table 1** shows how the pivotal measures map on to the specific objectives.

[112] Directive 2001/83/EC merged 11 prior directives related to medicinal products, and together with the Regulation (EC) No 726/2004, consists of 220 articles, offering numerous "levers" to adjust the policy.

[113] To give an example, a pivotal measure to support market access is making the last 1 or 2 years of regulatory data protection subject to market launch in all EU countries and this is discussed in the main body of the IA. Access in all Member States will be supported by other measures, such as facilitating multi-country packs to make launches in smaller Member States easier, but those measures are rather considered in Annex 11.

5.2.1 Tabular overview of policy options

Table 1 Mapping of **pivotal elements** to the **specific objectives**

Objective	Baseline	Option A	Option B	Option C
Promote innovation, in particular for unmet medical needs.	8 years DP +2 years MP	8 years DP +2 years MP Special incentive: +1 year DP for medicines that address UMN +6 months DP to include comparative trials Digitalization, simplification elements from horizontal measures	6 years DP +2 years MP Special incentive: + 2 years DP for originators that address UMN. Digitalization, simplification elements from horizontal measures	6 years DP +2 years MP Special incentive: +1 year DP for medicines that address UMN + 6 months DP for comparative trials Digitalization, simplification elements from horizontal measures
Incentives to promote the development of novel antimicrobials	No special incentives for the development of antimicrobials	Transferable exclusivity vouchers for antimicrobial products	Pay or play model for antimicrobial products	Transferable exclusivity vouchers for antimicrobial products
Create a balanced system for pharmaceuticals in the EU that promotes affordability for health systems while rewarding innovation	Generic and biosimilar entry after DP/MP periods are over providing a predictable framework for competition from generic and biosimilar medicines.	Baseline + additional rewards for innovation and access. Comparative trials may lead to public cost savings.	Earlier entry of generics and biosimilars with 2 years shorter protection than baseline +2 years MP for medicines with no return on investment. Require public transparency on any relevant public contribution or funding, including of research and development costs	If market launch condition not met, earlier entry of generics and biosimilars Require transparency on public contribution to R&D costs in relation to clinical trials included in the MA application Comparative trials may lead to public cost savings.
Ensure access to innovative and established medicines for patients with special attention to enhancing security of supply across the EU	Currently no obligation or incentive to launch in a particular or group of MS	+6 months additional protection period if centrally authorised product is placed on market in all MSs within 6 years of the MA (milestone incentive); and allow generic competition if not launched in majority of MS within 5 years of MA (disincentive)	Obligation to place a centrally authorised medicine on the market in the majority of MS (small markets included) within 5 years	+2 years (or 1) DP extension if medicine is placed on all EU markets within 2 years of authorisation and appropriately and continuously supplied
	Obligation to notify a withdrawal 2 months before the interruption in market supply of the product	Notification requirement same as in baseline	Notification requirement same as in baseline	Improve data on medicines shortages, through adequate notification periods for withdrawals and serious shortage risks; shortage prevention, increased transparency of the supply chain, mitigation plans for all medicines and stockpiling of critical medicines Monitoring of shortages is reinforced with a mechanism of information exchange between MS.
Reduce environmental impact of the pharmaceutical product lifecycle	An ERA is required for all new MA applications. Potential risks from medicines to the environment are assessed by regulators and precautionary measures are taken	Same as baseline ERA	Strengthen the conditions of use for medicines and ERA requirements, including the assessment of the environmental risk of manufacturing and its impact to AMR	Same as option B with the inclusion of AMR aspects in GMP.
Reduce regulatory burden, and provide a flexible regulatory framework	Not applicable / non legislative measures	Horizontal measures* *The horizontal measures are applicable to all options, for details please refer to section 5.2.5.	Horizontal measures*	Horizontal measures*

Notes: AMR=antimicrobial resistance; DP=data protection; EMA/HMA= European Medicines Agency/Heads of Medicines Agencies; ERA= environmental risk assessment; GMP=good manufacturing practice; MA= marketing application; MP=market protection; MS=member state; R&D=research and development; UMN=unmet medical need

5.2.2 Policy Option A

Option A addresses the identified problems through **incentives** rather than setting further obligations coupled with a stronger enforcement of existing obligations and information requirements.

To stimulate **innovation**, Option A maintains the current system of regulatory incentives (8 years data + 2 years market protection), supplemented by a targeted incentive, an additional 1 year of regulatory data protection for products addressing unmet medical need (UMN). Clarifications of the scope and new definitions should facilitate innovation. It also foresees the introduction of a new **incentive for the conduct of comparative trials**, which bring a more robust evidence base for the assessment of effectiveness of new treatments and facilitate decision-making downstream in the lifecycle of medicines.

Option A stimulates the development of novel **antimicrobials** that can fight resistant pathogens through **transferable exclusivity vouchers**. A transferable regulatory protection voucher (transferable exclusivity voucher) allows the developer of a novel antimicrobial that reduces AMR to benefit from an additional year of RP on another product in their portfolio or sell the voucher to another company. This is a measure supported mostly by industry as a way to underpin the substantial R&D costs of bringing new classes of antimicrobials to the market[114]. This will be supported by measures on harmonisation of the summary of product characteristics for nationally authorised antimicrobials to support good prescription practices.

Option A promotes patient **access** with a 6 month regulatory data protection incentive if a product is placed on the market in all Member States within 5 years of MA. The rationale behind the measure is that MAHs can be encouraged to increase the number of markets in which they launch products or accelerate the timeframe within which they do so, by offering them a reward in exchange.

Measures on **security of supply** retain the current requirement for notifications of withdrawals (at least two months in advance).

The current **ERA requirements** continue with an additional obligation to include the information on the environmental impact of supply chain actors in the application dossier. The latter proposal is part of the package of suggestions to support quality and manufacturing aspects (QMC) for medicines.

Among the **non-pivotal measures** of Option A are a non-binding system for scientific assessment of evidence for repurposing off-patent medicines to include new indications for allow for innovation, measures to facilitate multi-country packs to enhance access and inclusion of new manufacturing methods into the framework to both ensure best quality manufacturing and to cater for innovation.

5.2.3 Policy Option B

Option B uses **more obligations** to address the specific objectives rather than incentives. This option explores stronger monitoring mechanisms and increased obligations with interventions at different milestones in the lifecycle of a medicine to foster patient access, affordability and security of supply.

To stimulate **innovation**, especially for unmet medical needs, it introduces a modulated **system of incentives**, with a reduction in the current standard regulatory protection periods. The new standard protection[115] for all originator medicines would consist of 6-years data protection and 2-year market protection. New originator medicines with a demonstrated ability to address UMN would benefit from an additional 2 years of data protection, thus maintaining the current baseline. Other medicines will be entitled to strengthened protection only if they can demonstrate no return on investment in view of investment costs, including for research and development.

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[114] Previously explored in the Joint Action on Antimicrobial Resistance and Healthcare Associated Infections.

[115] Baseline protection is the current regulatory protection of 8 years of data protection and 2 years of market protection which also applies in Option A; (new) standard protection is the regulatory protections of Options B and C of 6 years of data protection and 2 years of market protection.

Option B also encourages the development of novel **antimicrobials** that can fight resistant pathogens through a 'pay or play' model. Either a company holds an antimicrobial in its portfolio, or it pays into a fund for financing the development of novel antimicrobials. It also includes measures for prudent use of antimicrobials including monitoring consumption, optimising package sizes and stricter rules for the use and disposal of antimicrobials for human use and tightening of prescription requirements for example through the mandatory use of diagnostics prior to prescription of antimicrobials thus target pathogens better.

Access measures in Option B consist primarily of an obligation to launch centrally authorised medicines on the market in a majority of Member States (small markets included) within 5 years. If the obligation is not fulfilled, the medicine loses its protection, and generics can enter the market.

Measures on **security of supply** encourage EU coordination for exchange of information and use existing guidelines and systems, such as the EU medicines verification system[116] to track supply, and measures to increase manufacturers' responsibilities to ensure supply. The notification period for withdrawals remains identical to the baseline and MAHs are obliged to offer their MA for transfer to another MAH in case of withdrawals from the market.

The **ERA requirements** and conditions of use for medicines are strengthened. This option also foresees the assessment of the environmental risk of manufacturing in the ERA as part of the marketing authorisation. Moreover, it proposes improving oversight of sites through modification of rules on inspections and a mandatory joint audit scheme for national GMP and GDP inspectorates.

Non-pivotal elements in Option B include the possibility for regulators to impose a post-authorisation obligation for comparative studies on the effectiveness of a given medicine compared with the standard of care. Codification of rolling reviews beyond crisis-related medicines, and measures to future-proof the regulatory system by reviewing the scope and definition of products that need to be accommodated under the pharmaceutical legislation and simplifying/clarifying the regulatory framework for certain categories of medicines (e.g. borderline products) should facilitate innovation. Anti-competitive practices such as introducing multiple marketing authorisations are restricted, interchangeability of a biosimilar medicine with its originator medicine will be elaborated in the product assessment and the Bolar exemption (legal exemptions from patent infringements for acts relating to the regulatory submission of testing data) will be broadened to facilitate generic entry. Together with obligation for all MA applicants to publicly disclose any relevant public funding received (R&D **transparency**) this should address **affordability**.

5.2.4 Policy Option C

Option C proposes a 'quid pro quo approach' with a modulated system of **incentives combined with obligations**.

The regulatory protection for originator medicines in option C is split into a standard and a conditional period. The standard is 6 years data protection and 2 years market protection (as in option B) while the conditional period is 2 years (or 1 year, see box below with a variation of the option). The conditional year/years are granted only if the product is placed on all EU markets within 2 years of authorisation and appropriately and continuously supplied thus increasing **access** to patients. To be pragmatic, the provision has some exemptions (e.g. the possibility for a Member State to waive[117] the obligation within its territory for the purpose of the incentive). For it to be predictable for generic and biosimilar companies, a time limit is set (i.e. 2 years before the DP expires) for a final decision on the prolongation or not. If a company fails to comply with the market launch requirement, there will be earlier generic competition and increased **affordability for health**

[116] Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products, OJ L 174, 1.7.2011, p. 74.
[117] In the case that a MS does not wish to be supplied at that moment.

systems[118]. Moreover, originator medicines addressing an UMN would receive an additional 1 year of data protection to stimulate more innovation in areas of unmet patient need.

The system of special incentives in options A and C are similar but transparency on public contribution to the costs of clinical trials will be required for all medicines in option C. There is a special incentive (6 months) to stimulate developers to conduct comparative trials. **Incentives can be cumulated**, however the total regulatory protection period is **capped at 11 years**, which is a difference compared to Option A.

Variation to Option C

Option C aims at a balanced mix of obligations and incentives, which in individual cases may result in a higher level of protection for companies than the current baseline. To mitigate this result, a variation[119] to Option C is assessed, where no medicine could reach a 'beyond-baseline' level of protection. The variation consists of a reduction of the conditional **2 years** protection period to **1 year**, and a capping of cumulated incentives at 10 years.

The next sections will consider Option C with 2 years conditional period as default. The differences in impacts between the default option C and the variation are discussed in section 8.1.

Variation to Option C
6 years DP + **1 years DP if placed in all EU markets** +2 years MP
Special incentives:
+1 year DP for medicines that address UMN
+ 6 months DP for comparative trials
Incentives capped at 10 years.
Transferable exclusivity vouchers for antimicrobial products

With respect to **innovation**, the changes to the scope, definitions and classification advice with regard to medicines and the codification of rolling reviews and PRIME would be similar to option B. However, this option also foresees the inclusion of a sandbox environment (i.e. a structured form of testing before formal regulation) which would more readily accommodate innovation in breakthrough areas where the current framework does not sufficiently cater for this innovation. A binding system for scientific assessment of evidence for repurposing off-patent medicines will be established, and obligations will be simplified to facilitate non-commercial entities (e.g. academic) to become marketing authorisation holders. To incentivise development of novel **antimicrobials** that can fight resistant pathogens, a system of transferrable exclusivity vouchers (as in option A) is explored. The fight against AMR is corroborated with a strong emphasis on prudent use measures which are similar to those proposed in option B.

With respect to **security of supply**, in addition to an EU definition of shortages, critical shortages and critical medicines, option C measures include a balance of EU- and Member State-level actions to mitigate and prevent **shortages** and build on the shortage provisions in the EMA reinforced role legislation[120]. The approach to reporting shortages is harmonised across the EU, while monitoring of supply remains with Member States and only critical shortages are escalated to EU-level. As with option B, support to the management of shortages is increased through earlier, harmonised reporting on shortages. There is the possibility of information sharing by Member States on critical shortages and supply chain vulnerabilities.

The **ERA requirements** are similar to option B. It would also strengthen conditions of use of medicines on a case by case basis to limit the environmental impact without affecting the

[118] An alternative consequence could be repealing marketing authorisation of companies not launching in all EU, however this would deprive patients' access to the concerned medicine, hence this measure was discarded.
[119] During the evaluation several stakeholders from patients' groups and academia argued that incentives are overly generous within the EU.
[120] Regulation (EU) 2022/123 of the European Parliament and of the Council of 25 January 2022 on a reinforced role for the European Medicines Agency in crisis preparedness and management for medicinal products and medical devices, OJ L 20, 31.1.2022, p. 1.

appropriate therapeutic use. It will include AMR aspects in GMP to allow a more holistic assessment of environmental risk along the pharmaceutical lifecycle.

With regard to **non-pivotal elements**[121], this option foresees stronger oversight of manufacturing supply chains through changes to inspections, reinforced Member State inspection capacity (joint audits of inspectorates) and increased EMA coordination. The strengthened Bolar provision to promote competition and hence **affordability** listed in Option B is retained and the transparency obligation on public funding is limited to clinical trials. Improvements to the current Hospital Exemption will continue allow for the use of ATMPs without marketing authorisation, but under stricter conditions to ensure quality, safety and efficacy of these therapies.

Transferable exclusivity vouchers and r*estrictions on their granting and use*

The transferable exclusivity voucher is a tool to **generate funds for the development of novel antimicrobials**. The analysis in section 6.1.1.4 points to the conclusion that even though vouchers can be an expensive solution, they represent a credible measure against AMR if applied under strict conditions; their benefits and costs need to be weighed against the cost of inaction and the impact of AMR on health and economy[122].

By setting strict criteria for antimicrobials that can benefit from the voucher, its value would be calibrated to benefit the developer of the antimicrobial more than the buyer. The analysis in section 6.1.1.4 explains why vouchers can work only if they are very restricted to a limited number (i.e. max 1 per year). This is also the reason why they score differently in the impact assessment for orphan and paediatric medicines where such limitation is not possible (see details in Annex 4).

To achieve strict limitations, only those medicines that are 'game changing' antimicrobials for reducing AMR can receive '**novel antimicrobial' status** by the Agency, based on clear criteria set out in the legislation. The antimicrobial is considered novel, and thus eligible for the voucher if preclinical and clinical data underpin a significant clinical benefit with respect to antimicrobial resistance and it either represents a new class of antimicrobials or it has a new mechanism of action that is distinctly different from the mode of action of any authorised antimicrobial (criteria to be assessed by qualified experts). Moreover, the active substance should not have been previously authorised in a medicinal product in the EU that addresses a multi-drug resistant infection or a serious or life threatening infection. This will also direct investment and research into those game changing products. Even if found eligible, additional supply requirements, transparency conditions on funding received and on the sale or transfer of the voucher and other conditions will be set in the legislation.

There would be moreover a review clause in the legislation to evaluate the application of the vouchers after some years and decide on the continuation or not of the measure. It may take some time until an antimicrobial is authorised that is eligible for a voucher, a voucher may not be used immediately after it has been granted and the effect of the extension of data protection due to a voucher may also take some time to be seen. Several vouchers have to be granted and been used to gain sufficient experience for a review of the measure.

5.2.5 Horizontal measures

All options are complemented by a series of horizontal measures. These are necessary to improve the effectiveness and efficiency of the regulatory system overall and will act on core elements of the authorisation and lifecycle procedures. They respond to the specific objectives of **innovation**, and **reducing the regulatory burden and providing a flexible regulatory framework**.

Generic marketing authorisations will be simplified by enabling a common assessment of manufacturing data across products, as generic medicines often source active substances from the

[121] See Annex 11 for details.
[122] AMR-Tackling-the-Burden-in-the-EU-OECD-ECDC-Briefing-Note-2019.Pdf

same site. A more efficient repeat use procedure[123] will be provided to reduce administrative and cost/burden and prevent medicine shortages. Furthermore, the sunset clause and renewal of MAs after five years will be abolished to simplify procedures. Likewise, the envisaged reduction in the number of notifiable variations reduces the administrative costs incurred by MAHs and regulators.

Provisions of the legislation will be reviewed with regard to novel combined products (e.g. where medicines are coupled with medical devices, software, or artificial intelligence). To address shortcomings highlighted in the evaluation[124] the legislation will ensure complementarity with the medical devices regulation/in vitro diagnostic regulation in relation to benefit/risk assessment, responsibilities of the medicine developer, and joint scientific advice.

In addition, delinking the environmental risk assessment of medicines that contain or consist of GMOs from the GMO legislation and replace it with GMO environmental risk assessment requirements and procedures adapted to the specificity of medicines under the general pharmaceutical legislation is considered, but these changes would not constitute a complete derogation from the GMO legislation.

New concepts will be integrated, such as adaptive clinical trials and full use of health data (real world evidence), applying the digital by default principle, notably through electronic submissions of applications, variations to MAs and electronic product information. The provision of authorised electronic product information for EU medicinal products would enable easier access to data contained within the product information, taking into account needs of patients, consumers and healthcare professionals, as well as the risk of digital exclusion.

The working methods of EMA and the European medicines regulatory network will be adapted, especially with regard to the functioning of the centralised procedure and the decentralised procedures, the use of expert assessment teams and multi-expert inspections teams to ensure a better use of the available network resources. The evaluation also identified suboptimal coordination between the EMA committees that duplicate work, create administrative burden and risking delays especially in the assessment of medicines for rare diseases and for children[125] and ATMPs. An EU-wide centrally coordinated process will be foreseen offering early dialogue and more coordination among clinical trial, marketing authorisation, health technology assessment bodies and pricing and reimbursement authorities for integrated medicines development and post-authorisation monitoring, pricing and reimbursement.

6 WHAT ARE THE IMPACTS OF THE POLICY OPTIONS?

6.1 Economic impacts

The general pharmaceutical legislation rewards innovators through the **regulatory data and market protection (RP)**. By protecting data on the safety and efficacy of the product, RP guarantees that during the data protection period no generic/biosimilar medicine can obtain a marketing authorisation referring to the originator's data. This effectively protects innovators from generic or biosimilar competition[126] for 10 or 11[127] years after authorisation. In comparison with other jurisdictions, the EU ranks high (see **Table 2)**.

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[123] See glossary.
[124] See Annex 5. The evaluation showed the need for more clarity on roles and responsibilities and for a more integrated approach in relation to scientific advice on medicines and medical devices.
[125] SWD(2020) 163 final.
[126] RP does not prevent companies willing to undertake their own clinical testing to seek marketing authorisation for the same medicinal product if they do not infringe on any patents or SPCs. However, that would be rather costly for entering a market, where the originator medicine is already present, and hence rarely occurs.
[127] An extra year is granted for an additional indication with significant clinical benefit. Historically around 1 in 8 medicines qualify for that.

Table 2 Basic regulatory protection periods for medicines globally[128]

Country	Protection	Duration
Canada	New Chemical Entity+ Market Protection	6+2 years
EU	New Chemical Entity+ Market Protection	8+2+1 years
Switzerland	New Chemical Entity	10 years
USA	New Chemical Entity (small molecule)	5 years
USA	Biosimilar Application Approval Exclusivity (biologic)	4+8 years
Israel	Market Protection	6 or 6.5 years
China	New Chemical Entity	6 years
Japan	New Chemical Entity	8 years

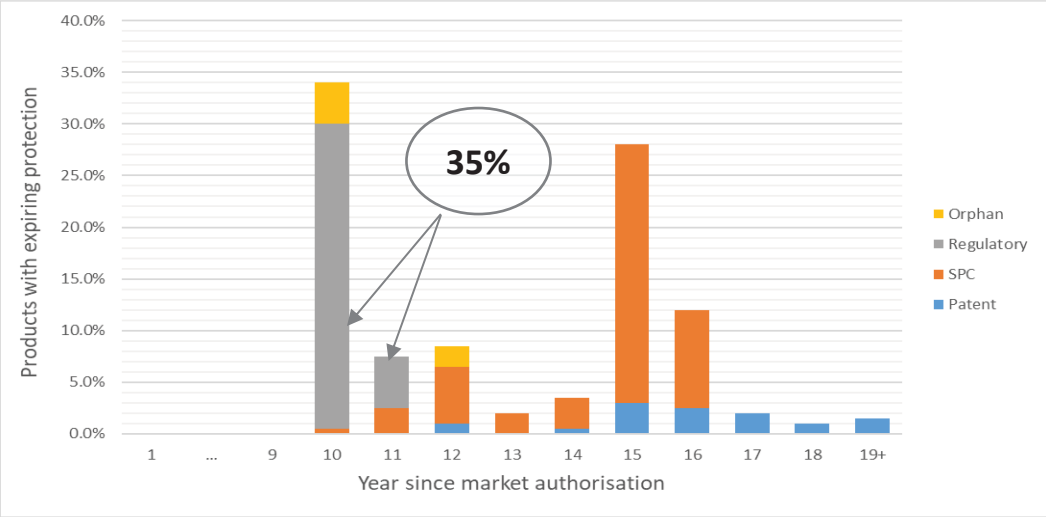
In addition to RP, medicines are also protected by patents (20 years), SPCs (up to 5 year extension of primary patent, but maximum 15 years from marketing authorisation), and medicines for rare diseases also benefit from 10 years market exclusivity (+2 years if paediatric studies were carried out)[129]. The patent and SPC protection start from the patent filing, and depending on the time until authorisation they may offer longer or shorter protection than RP. It differs case by case which instrument provides the longest protection period after entering the market, as demonstrated by **Figure 3** on a representative sample of 200 medicines. Medicines protected by patent or SPC not only enjoy a longer protection, but on average they generate 2-3 times higher revenues than those protected only by RP (Table 3).

Table 3 Medicines' protection period and revenues by their last layer of protection

Last line of protection	Number of products	Avg. protection duration	Avg peak annual sales[1]
Regulatory protection	69	10.1 years	**€ 158.7 m**
Market Exclusivity	12	10.7 years	**€ 41.7 m**
SPC	95	14.3 years	**€ 368.3 m**
Patent	23	16.7 years	**€ 300.5 m**
Grand Total	**199**	**12.9 years**	**€ 268.2 m**

We expect this ratio among protection types to remain in the next 15 years, therefore the changes to the RP would **concern around 1/3 (i.e. 35%) of the new medicines**, which have a **23% share among all originator medicine sales in the EU**.

Figure 3 – Ratio of medicines by the length of last layer of protection and type of protection

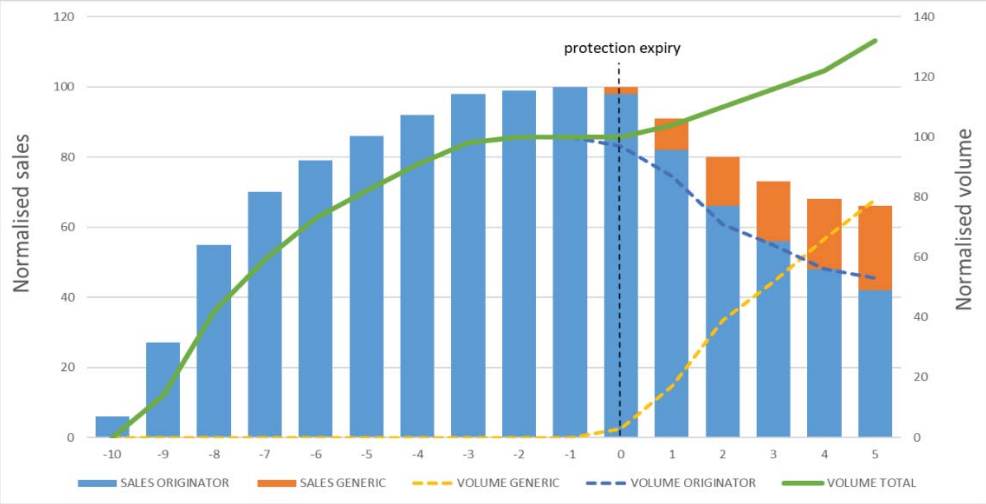


We provide a conceptual model to explain the economic impacts of the changes in the RP, on the different stakeholders. The model is based on the commercial lifecycle of a representative innovative

[128] Data collection by Technopolis Group, 2022.
[129] A diagram with the current regulatory and IP protections in the EU can be found in Annex 9.

medicine, an analogue, for which RP is the ultimate protection. To create this analogue, historical data[130] were examined, and the evolution of sales followed from market authorisation until protection expiry, and 5 more years from then, along with generic/biosimilar sales, **Figure 4**. The model uses normalised units to represent prices and volumes across different products, where 100 is equal to originator's peak sales, at year -1. It is assumed that the pricing strategy of the manufacturers remain unchanged. The calculations were done based on the public, list prices (not the actual, confidential prices).

Figure 4 Normalised sales and volume for products with 8+2 years of RP protection (baseline)



The SPC evaluation[131] highlighted that generic competition is not uniform across medicines. High-sales medicines, small molecule medicines are more likely to be contested and by more competitors, leading to quick erosion of the price and the innovator's premium. On the other hand, biological medicines, medicines for rare diseases and low revenue products are less likely to be contested, resulting in slower price erosion, or even maintaining a monopoly position. To account for this variability, the model considers the average evolution of sales volumes and values across all the RP-protected medicines in a nine-year cohort, including those medicines that were not contested by generics after protection expiry. The model represents well real-life at systemic level, even though some medicines – for example, those that face a high number of competitors – might show a much steeper erosion, whereas others might see persistently high sales after expiry in the absence of competitors.

From year 0, the generic medicines enter the market with a lower price, carve out a growing market share and force the originator to offer discounts[132]. The volume of generic medicines steeply increases, partly because some users substitute the originator medicine with generics and partly because the total volume rises with increased affordability. For health systems, the price drop following generic competition means cost savings. In our analogue, the price drop is 50% on average at year +5. The lower price extends eligibility and more patients and from more Member States can have access to the medicine either in its original or generic form. Even with the 32% more patients served at year +5, health systems pay 34% less than at peak sales in year -1.

To account for the impacts of modifying the RP, we use the above baseline and the 16 years observation period, which we consider as the commercial lifetime of an RP protected medicine. This allows to understand how the stakeholders' positions change under the different scenarios. Extending the protection allows innovators to seek longer monopoly rents, but it delays cost savings

[130] A cohort of medicines approved between 2004 and 2011, where RP is the last defence. Further explanation of the inputs used for the model is provided in Annex 4.
[131] SWD(2020) 292 final.
[132] The evaluation (Annex 5) found that originator products can maintain a 30% premium over their generic competitors.

and broader access for the public and delays revenues for generic companies. Decreasing protection has the exact reverse effect.

Profit, sales, cost, volumes – how we measure economic impacts for key stakeholders

For **health payers** we measure the impact of changes by the change in the **cost of medicines**, which can be directly deducted from total sales of originator and generic medicines in IQVIA data.

For **patients**, we measure the impact of change by the change in the **volume of medicines**. The more the volume, the more patients could benefit from therapy, either using originator or generic product. We will indicate the monetary value of the volume difference as "Δ of patients treated (monetised)".

For **originator** and **generic industry** the key measure of impact is **the profit** that they can realise from their business operations.

There is no readily available dataset on profits but we have good data on sales (revenues) from the IQVIA database. By deducting the cost of sales from the revenues, we can calculate the gross profit. The gross profit only includes the variable costs of manufacturing and distribution, but not the fixed costs, such as R&D and investment in infrastructure. In our model we distinguish three categories of revenues, each with a different margin of gross profits.

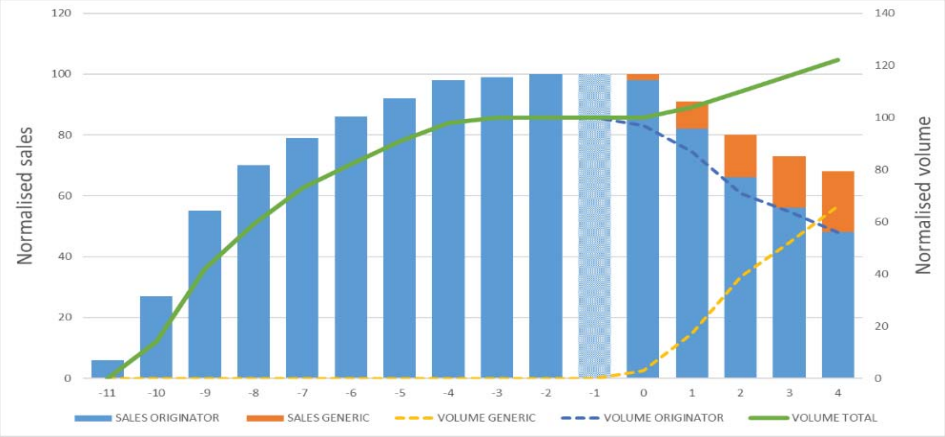
- **Protected originator sales**: this is the most profitable category during the protected period of new medicines. Based on a sample of reports from publicly listed companies we apply a 80% gross profit margin on the revenues (20% cost of sales)
- **Contested originator sales**: once generics enter the market, originator products are forced into price competition. Still, originator products can maintain a price premium compared to generics albeit reduced thanks to brand loyalty and strong sales force. We assume a 50% gross profit margin in this category.
- **Generic sales**: generic industry operates on a high volume, low margin basis. With low product development risk, a lower profit margin can be sustainable. We apply a 33% gross profit margin on generic revenues.

6.1.1 Economic impacts of key policy measures

6.1.1.1 Special incentives through increasing regulatory protection (Option A and C)

To understand the economic impact of an increased regulatory protection (either offered for UMN, comparative trials or market launch) we have added an extra year of protected sales to our model, and analysed the gains/losses for the different stakeholders during the observed 16 years (**Figure 5**).

Figure 5 - Normalised sales and volume for products with 8+2+1 years of RP protection



The longer protection translates into higher profits for the innovator but increases the costs for patients and payers, and also delays revenues for generic manufacturers. Overall, payers, patients and the generic industry share the burden of allowing longer streams of monopoly revenues to the innovator, to compensate for extra costs occurred (comparative trial, market launch), or to reward and incentivise innovation of high public health benefit (UMN). The exact monetary impact depends on the length of additional protection, and on the number of medicines expected to benefit from a certain incentive. Below we assess the special incentives one by one.

Special incentive: 1 year extension of RP for medicines addressing UMN (Option A, C)

This measure affects RP protected medicines as last protection, altogether 35% of all new medicines. Of these we expect 15-20% to address UMN. Applying these rates on the 45 annual new authorised

medicines as per our dynamic baseline, **on average 3 special UMN incentives per year are expected**. It is worth noting that for orphan medicines too an incentive for high unmet medical needs is foreseen, extending the market exclusivity period beyond the modulated RP protection for those orphan medicines.

Table 4 – Impact of change of +1 year regulatory protection for UMN

1 year increase in RP	Product level change	Systemic change (3 medicines)
Originator gross profit	**+€94m**	**+€282m**
Generic gross profit	-€13m	-€39m
Cost to public payer	+€54m	+€162m
Patients monetised gains/losses	-€28m	-€84m
Patients + payer monetised gain/loss	**-€82m**	**-€246m**

Table 4 summarises the monetary gains and losses of the different stakeholders at a single product level, and also at systemic level, counting with 3 incentives a year. For affected medicines, the **innovators'** gross profit will increase by €282m a year, and the incentives would increase the cost for payers by €162m. Taking into account that some patients will not have access to the medicine due to the sustained higher price, the total **cost will be €246m to the public**.

In exchange for this public cost, the UMN incentive would directly reward investment in UMN R&D and likely would have a spill-over effect: national and EU-level research and innovation funding could be specifically channelled to UMN, and national pricing and reimbursement systems could differentiate the UMN addressing medicines, making them even more viable commercially.

We expect that the incentive would attract more investment in UMN and **result in 1-2 additional UMN medicines per year**, for the benefit of the patients and creating savings for the health systems. This important and non-monetised[133] benefit has to be seen together with the costs.

The consultations showed that both public authorities and patients support modulating the RP periods around factors such as UMN. Industry on the other hand said that if incentives were limited to UMN only, that would disregard the reality of science and incremental innovation and would introduce uncertainty for businesses as the ultimate duration of the regulatory protection period would not be fully clear when their investment decision is made[134].

Special incentive: 6 month RP extension for comparative clinical trials (Option A, C)

Similar to the previous incentive, this measure could benefit medicines for which RP is the last layer of protection, making around **35% of all new medicines eligible**. Conducting comparative trials may not be feasible for some medicines, and if the cost of the comparative trial is too high as opposed to the reward, companies will decide to decline the incentive. Taking these factors into account, we expect that half of the RP products or **8 medicines annually** could benefit from the incentive. Table 5 shows the economic impacts on the main stakeholder groups of this incentive both at individual product level and at systemic level, for the 8 medicines per year.

Table 5 – Impact of change of +6 months year regulatory protection for comparative trials

6-month increase in RP	Product level change	Systemic change (8 medicines)
Originator gross profit	**+€47m**	**+€378m**
Cost of comparative trial for originator	**+€35m**	**+€280m**
Generic gross profit	-€6.5m	-€52m
Cost to public payer	+€27m	+€218m
Δ of patients treated (monetised)	-€14m	-€112m

[133] Monetising the benefits of an additional new medicine has several challenges: there is a large variation between medicines' value, defined by the patient population and severity of disease. Moreover, monetising a medicine's value requires putting a monetary value on patients' life and health, as well as on the physical and emotional burden of their families and carers. We thus have chosen not to monetise these impacts, but quantify them as much as possible.
[134] See Annex 14 for further details on the factors influencing access and affordability.

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

Comparative clinical trials have a cost. In the absence of publicly available data, we estimate the cost of a comparative clinical trial at €20-50m (the model uses the middle value of the range), referring to the paediatric trials as a benchmark[135]. Due to the revenue extending nature of the incentive, higher sales medicines would have a higher compensation, independent from the cost of the trial.

For the public, 8 trials a year would cost €328m, but at the same time it would generate important non-monetised benefits: comparative trial data will enable public authorities making better informed reimbursement decisions and saving cost down the line. Data from trials would also accelerate pricing and reimbursement decisions, allowing faster access to patients.

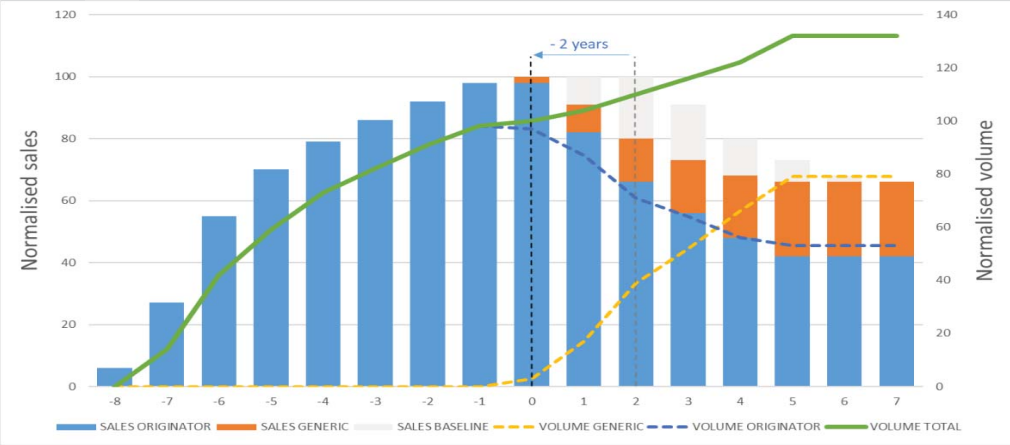
In the consultations, industry stated that comparative data is already provided at authorisation stage when possible and that some products (e.g. ATMPs, products for ultra-rare diseases) will not benefit from this incentive. Patients and public authorities on the other hand supported comparative clinical trials (even as an obligation in the case of the latter).

6.1.1.2 Decreasing standard regulatory protection (Option B)

A key feature to support affordability in Option B[136] is a decreased regulatory protection, from 8+2 years in the baseline to 6+2 years, except for a minority of medicines: UMN addressing medicines and medicines with no return on investment can maintain 8+2 years RP.

To model for the change, we removed from our analogue the original year -1 and -2, enabling earlier generic competition. To keep the same 16 years of observation period, we have added year +6 and +7 in the model, which we assumed to be equal to year +5[137] (**Figure 6**).

Figure 6 - Normalised sales and volume for products with 6+2 years of RP protection



This measure would only concern medicines that have RP as the last layer of protection, about 1/3 of the 45 new medicines. Out of this 15 medicines, 20% may be UMN addressing or low revenue thus exempted from the measure. Some of the RP protected medicines are eligible for SPC protection between year 8 and 10 from market authorisation, partially offsetting the RP reduction. Overall, **9-12 medicines may be affected** by the reduction annually. **Table 6** summarises the impacts at product and systemic level for the different stakeholders.

Table 6 – changes between baseline and RP 6+2 per stakeholder

2 year decrease in RP	Product level change	% change	Systemic change (9-12 medicines)

[135] The joint evaluation of the orphan and paediatric regulation estimates the cost of paediatric studies at €22m.
[136] This section discusses Option B solely, the eventual loss of protection in Option C for some medicines not complying with the access condition is discussed in 6.1.1.3.
[137] More on the assumptions in Annex 4.

Originator gross profit	-€188m	**-15%**	**-€1.97 b**
Generic gross profit	+€25m	+56%	**+€266 m**
Cost to public payer	-€107m	-6%	**-€1.13 b**
Δ of patients treated (monetised)	+€71m	+5%	+€745 m
Patients + payer monetised gain/loss	+€178m	+9%	**+€1.86 b**

Compared to the baseline, affected **originators** would lose their two highest-revenue, most-profitable years. The product would **lose 15% of its lifetime profits**. For the originators this sums up to €2bn loss annually in gross profits from the EU. More than 75% of originators replying to the targeted survey expressed a negative stance towards a reduction of protection period for products that do not address an UMN.

On the other end, the measure would generate €266m additional gross profit for the generic industry, and €1.13bn direct cost reduction for health payers. Thanks to the lower price, 5% more patients could benefit from the concerned medicines and accounting for the extra patients served in a monetised form, the total benefit for the public is €1.86bn, or 0.9% of the total EU pharmaceutical expenditure. An additional benefit would be a higher proportion of UMN among newly approved medicines, due to the relative higher reward.

Because of all the other co-existing protections (SPC, patent, market exclusivity), option B **would leave 75-80% of new medicines unaffected. The saving for payers and patients, would be borne by a dozen of medicines, which would lose 15% of their profits.**

Apart from the imbalanced impact, the measure would have additional costs. With a lower reward, some developers may decide not to enter the EU market, or delay entry and seek return on other markets first. An estimated **€670m will be lost for innovation**[138] that could benefit patients.

Even though in the consultation civil society organisations in principle supported a reduction of regulatory protection, patients would pay the highest price for the lost innovation, in that their medical needs could not be met. Innovation is important for health payers too if new products offer cost-effective health solutions, and a continuous stream of innovative medicines is needed for the generics industry for new business opportunities.

Would the RP reduction harm EU competitiveness?

A direct link between EU incentives and EU competitiveness is hard to establish because while the incentives make the EU markets more attractive, they are agnostic to the medicines' geographical origin. Around 20% of new medicines authorised in the EU are from the EU, the others are mainly from US, UK, Switzerland and Japan that are equally eligible to all EU incentives. Equally EU based innovative companies can benefit from incentives elsewhere, if they sell their products there.

In June 2016, the Council requested the Commission to conduct an evidence-based analysis of the impact of incentive mechanisms, notably SPCs. Two studies have been commissioned. One from Max Planck Institute[139] questions whether the availability of patent or SPC protection affects companies' decisions to locate research facilities in one jurisdiction or another, emphasising that other factors are likely of greater importance. The Copenhagen Economics study[140] argued that SPCs could play a role in attracting innovation to Europe, pointing out that taxation, education, and other factors are probably more significant in that respect.

[138] 20% of lost protected sales, the typical R&D rate of revenue for originator companies, calculated in Annex 4.
[139] Max Planck Institute. Study on the legal aspects of supplementary protection certificates in the EU, 2018.
[140] Copenhagen Economics. Study of the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards, 2018.

6.1.1.3 Measures to improve market access (Option A, B and C)

All policy options address the challenge of unequal market access to new medicines across the EU but with different measures. As all options modulate RP, they all would impact those medicines that have RP as the last layer of protection, 35% of new medicines, **15-16 medicines a year**. Option A offers a +6 months RP extension incentive for medicines launched in all EU markets within 5 years of authorisation. Option B instead requires companies to launch their product in the majority of all EU countries within 5 years, otherwise they lose their protection and generics are allowed to the market. Option C requires market launch in all EU MS (except those not interested in the product) within 2 years of authorisation as a conditionality to parts of the protection period. Complying medicines would gain 2 years of conditional RP (or 1 year in the case of the variation of Option C).

We have also observed a strong correlation between a medicine's peak sales and its access across EU countries. The magnitude of the incentive or the loss of protection is commensurate to the peak sales, meaning that for high sales medicines the motivation is very high to comply. Since high-sales medicines are launched already in most of the markets, for them the compliance cost is small. The opposite is true for low sales medicines.

Based on the size of the incentive (or potential loss in option B and C), the compliance is estimated as the percentage of medicines fulfilling the market launch requirements. From this, the costs or savings to the public have been calculated (**Table 7**). For option A, we used the same model as for the special incentive for comparative trials, but expecting that only the higher sales medicines would comply, a higher average peak sales was used in the model (detailed in Annex 4).

In option B and C the concept is reversed. If a medicine complies with the requirements, the stakeholders' position do not change. But non-complying medicines would face earlier generic competition, resulting in losses for originators and in gains for the public and generics. To calculate public savings stemming from non-complying medicines we used the model of the decreasing standard regulatory protection (section 6.1.1.2). Again, the average peak-sales value was adjusted, assuming that the low-sales medicines will be the ones not complying.

Table 7 – Comparative table of measures improving access

Option	Expected compliance	Originator's reward/loss	Cost/benefit for public
Option A +6 months, if in all EU	50% (6-8 medicines)	+€527 m gross profit +7.5% gross profit for 7 complying medicines	+€455 m public cost
Option B -5 years, if not in majority of MS	75% (11-13 medicines) Majority of markets	-€842 m gross profit -34% gross profit for 4 non-complying medicines	€681 m gain from non-complying medicines
Option C* -2 years, if not in all EU	66% (10-12 medicines)	-€469 m gross profit -15% gross profit for 5 non-complying medicines	€444 m gain from non-complying medicines

* The differences in impacts between the default option C and its variation are discussed in section 8.1

To determine compliance we use assumptions and this inevitably carries uncertainties. Originator industry is better off with higher compliance and worse off with low compliance, which then results in profit losses. For the public, high compliance is the desired outcome, resulting in faster and increased access. However, non-compliance lowers the cost by shortening the protection period and thus contributes to affordability, also an improved outcome compared to the baseline.

The access measures benefit society, above all patients. These benefits are elaborated in the social impacts section (6.2). Option B has the disadvantage that it is unpredictable. Until reaching 5 years on the market, the generic industry will not know for sure whether the originator medicine complies or not. If generic companies prepare for non-compliance, and start development and production, the innovator's compliance would delay their entry by 3 years. And in case of non-compliance without the generic companies being prepared, there will be no generic competition for quite some time, neutralising part of the expected impact of the measure.

Practical details and impact of modulation of data protection for market launch (option C)

The access conditionality would be a first-of-its-kind policy measure that addresses a problem specific to the EU, and the primordial goal of it is to increase and accelerate EU patients' access to new medicines, regardless of the country they reside. The measure is successful if it is widely used and a high proportion of new MAHs comply with the requirements and benefit from the incentive. A low success rate would discourage companies and would not achieve access in all Member States.

Lack of access in a particular Member State can have many reasons. Sometimes companies decide not to launch or delay launch in a market because of low profitability, small patient populations, perceived cumbersome procedures, pricing policy, parallel trade. In other cases, Member States deny access because no therapeutic value is seen, the medicine is not cost-effective according their HTA assessment, or it would have an unbearable budget impact. There may also be objective roadblocks, such as the need for highly specialised delivery infrastructure or diagnostic tools for the therapy that do not exist in the Member State.

The proposed measure in option C targets companies to do their utmost to launch the medicine in all EU markets within a specific period after authorisation (e.g. 2 years) and ensure a continuous supply. This includes that companies shall file for pricing and reimbursement in all 27 Member States, they have to conduct negotiations in good faith, and upon positive decision ensure supply that covers the Member States' needs[141]. However, companies could still receive the market launch incentive if due to reasons beyond their control the market launch is delayed or not happened at all (e.g. the Member State doesn't wish to be supplied at that particular moment or doesn't have the specialised infrastructure e.g. in case of orphan medicines or ATMPs).

The Commission would grant the extra protection (2 years or 1 year for the variation to option C) based on a system where Member States will be obliged to confirm within a certain period after marketing authorisation compliance with the conditions of the incentive, justify a refusal by a statement of reasons based on objective and verifiable criteria or give a waiver to the company. Non reaction of a Member State will be considered as tacit confirmation of compliance.

Companies should not find it difficult to comply with the conditions of this incentive, as EFPIA already made a voluntary commitment[142]: their members would file for pricing and reimbursement in all EU27 Member States within 2 years from authorisation. This is already a step forward from the current situation, but it is voluntary, restricted to EFPIA members and there are no controls in the system. Hence, it does not work to the extent of the incentive, which relates to actual launch and supply not just filing. The proposed measure adds a significant financial incentive for complying, and it can also prevent dishonest applications[143]. By making ignoring certain markets or abusive negotiating practices very expensive, Member States, and especially smaller Member States would have a more balanced position when dealing with global firms.

The instrument to work adequately would also require Member States to act timely and in good faith, because if compliance is made unduly difficult and unpredictable, the access goals will not be met. Considering the common goal of both industry and Member States to ensure wide patient access in the EU, we expect this change to contribute positively to the negotiations between the two parties and that blocking the incentive will indeed be reserved to the objectively justified situations. Ultimately, any alleged abusive behaviour can be subject to judicial control at Member State level and a revision clause could be built in to take stock of performance after a certain time.

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[141] The Transparency Directive allows 180 days for Member States to make their pricing and reimbursement decision, therefore filing at 18 months shall allow a market launch in 2 years.

[142] EFPIA Access to medicines (efpia.eu)

[143] We have seen examples in the past that a small member state was offered 4-6 times higher price than Germany.

The specific situation of **SMEs and not-for-profit entities** and their capacity to engage in multiple parallel pricing negotiations will be taken into account by allowing longer period to comply with the market launch conditions, **3 years from authorisation**.

We can expect this measure to spur a **long term behavioural change** of both industry and public actors to engage more towards increasing access, which is a strong demand from public authorities and citizens. Ideally, launching new medicines in all 27 Member States in a timely fashion would be the standard for all medicines, and not only for the 35% of them (with RP as the last layer of protection) that are directly affected by the incentive.

Such incentive has not yet been tested on the market, however stakeholders were willing to share their views about it. Public authorities in the targeted survey and a workshop were overall positive to linking incentives with market launch, while industry was against. For industry, access depends on factors that are not under their control (e.g. variations in national reimbursement decisions); however, they agreed that the measure can be a financial incentive to launch in smaller markets. To address this concern, the design of the measure includes the safeguards explained above. Civil society organisations, patients, researchers and public authorities considered this measure as very important. They stressed the need to provide 'real' effective access and continuous supplies. Some public authorities argued that this measure should be an obligation. Member States have highlighted in a series of Council conclusions[144] that incentives need to be proportionate to the goal of encouraging innovation while improving patients' access to innovative medicines. They considered that deferred or missed market launches, and business behaviour, including high priced essential medicines pose a high burden for patients and health systems. They called the Commission to evaluate the system and take action.

Would a decreased protection translate into price increase?

Companies may try to increase prices to compensate for a shorter RP if they do not get the incentive, however, this will result in lower volumes sold, less Member States and fewer patients could afford the increased price. Rationally behaving companies should not have different pricing policies because of the length of protection, a higher price does not automatically lead to higher profits[145].

The Evaluation[146] compared prices of the top-selling almost 200 medicines in the EU, US, Australia, Canada, Japan and Switzerland. **We could not find any correlation between the prices and data protection periods**, however in the US prices for the same medicines are often 3-5 times higher than in other countries despite offering very long effective protection[147].

6.1.1.4 Measures addressing AMR (Options A, B, C)

Annex 15 describes innovative financing solutions – outside of the general pharmaceutical legislation – introduced in some EU Member States and some international initiatives to incentivise development of new antimicrobials.

Pay or play model (Option B)

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[144] Council conclusions on strengthening the balance in the pharmaceutical systems in the EU and its Member Stateshttps://www.consilium.europa.eu/en/press/press-releases/2016/06/17/epsco-conclusions-balance-pharmaceutical-system/; Council conclusions on innovation for the benefit of patients: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52014XG1206(03)&from=SK; Conclusions on strengthening the European Health Union: https://data.consilium.europa.eu/doc/document/ST-14029-2021-INIT/en/pdf

[145] A recent and extreme example is the case of Zynteglo®, a gene therapy authorised in the EU in 2019. The company insisted on a high price (more than €1m) that not even the richest markets were willing to pay, and led to zero sales and zero profits in the EU market.

[146] Notably the indicator AFF-1.2 on p100 of Annex 10, Analytical report.

[147] On the other hand, more new medicines and much faster than in the EU are made available to US patients, at least for those who can afford a premium insurance scheme.

In this model, a company co-finances the innovation and either holds an antimicrobial in its portfolio or it pays to a fund to finance the development of novel antimicrobials. A recent analysis[148] found that a pay or play model would impose additional costs on EU pharmaceutical businesses with the risk that the costs would be passed on to health systems (insurers and/or patients) through higher prices and while a minority may look to avoid a levy by developing antimicrobials or acquire businesses with an antimicrobial in the portfolio, the majority would likely view the surcharge as an unavoidable cost to be factored into their wider pricing policies. In addition, the fund would generate only limited amount of money so that only a limited number of rewards can be ensured. The results of this model could be seen only after several years (when the fund collects enough capital).

The pay or play model would not directly increase the number of novel antimicrobials and may increase prices of other medicines, creating substantial social costs. The benefits of the incentive would depend on the use of the collective fund, which is beyond the scope of the general pharmaceutical legislation.

This measure was supported by patients and other civil society organisations in the public consultation. Industry was the least supportive, they raised concerns that the model would unfairly penalise companies (particularly SMEs) with no expertise in AMR product development.

Transferable exclusivity vouchers for novel antimicrobials (Options A and C)

These would benefit in particular SMEs as they would be rewarded as early as regulatory approval for a new antimicrobial. It would also increase the attractiveness of the field for private financing mechanisms, such as venture capital. According to EFPIA[149], the value of such voucher in the EU should be between €280 m and €440 m per product, based on assumptions around a "fair European share", a proportionate contribution of the EU towards the development of a novel antimicrobial product that would benefit the global population. The voucher could be an important part of the EU response to AMR for the **development of novel antimicrobials**, i.e. not just products that are already in the (weak) pipeline. Such response could also include other initiatives, outside the legislation, such as joint procurement for antimicrobials under HERA to **guarantee revenue** paid to producers **for ensuring access** to existing or new antimicrobials.

Cost and benefit of transferable exclusivity vouchers

To understand the impacts of a voucher, the model of RP extension has been used, with some adjustments. The buyers and thus users of the vouchers would be companies that hold the products with the highest sales among the RP protected medicines. The commercial lifecycle of these products differs from the average, as their market is more attractive for generics/biosimilars. It results in a faster erosion of price and sales, therefore an additional year of protection has a higher value for the originator, and a higher cost for the other stakeholders. We have examined over a 10-year period the highest selling RP protected medicines, and identified the champions for each year. We used in our model a €545 m average peak annual sales for these champions (More details on the model in Annex 4). **Table 8** summarises the effects to the various stakeholders.

Table 8 – Changes to baseline with the voucher and value of voucher

Stakeholder	change	change %
Originator gross profit	**+€387 m**	+10.1%
Generic gross profit	**-€54 m**	-23%
Cost to public payer	**+€283 m**	+4.7%
Patients monetised gain/loss	-€158 m	-3.8%
Patient + payer monetised gain/loss	-€441 m	-7.3%

[148] (https://academic.oup.com/cid/article/71/8/1994/5736365?login=true).

[149] Representative of innovative industry: A new EU pull incentive to address Anti-microbial Resistabce (AMR) Recommendations from EFPIA.

The €545m gain of the originator in protected sales is not equal to the value of the voucher for the originator, because the revenue contains the cost of manufacturing and distribution, as well as the cost of capital. We assume that the originator can only use the voucher 2 years after buying it, to ensure that generic competitors can prepare for a delayed entry. Assuming 20% cost of sales and 10% annual cost of capital over 2 years, the **value of the voucher for the originator is € 360m** at a **cost of € 441m for payers and patients** (or €283m in nominal value, disregarding patients' loss).

Sharing the value of the voucher between buyer and seller

We were able to identify the likely average value of the voucher, however it remains uncertain what proportion of the value will be transferred to the seller – the actual developer of the rewarded antimicrobial, often an SME. The negotiating position of the seller will depend on the second highest selling medicine, the next potential buyer, similar to an auction where the winner has to pay only a little more than the second highest bidder. The situation is further complicated if there are more vouchers on the market and the EFPIA paper estimates 1-3 vouchers per year. Each additional voucher drives down the price for all vouchers in that year, as they generate competition for each other. For instance, if there are 3 vouchers, the price for all will fall between the value of the voucher for the 3rd and 4th best seller medicine. Using historic data on the second, third and fourth best-selling RP protected medicines in a given year, we can visualise the impact. (**Figure 7, Table 9**).

Figure 7 Distribution of buyer and seller advantage if 1 or 3 vouchers issued a year

Table 9 – share of value among buyer, seller and the public

1 voucher		**3 vouchers**	Voucher 1	Voucher 2	Voucher 3	Total
Seller rent	**€205 m**	Seller rent	€89 m	€89 m	€89 m	**€267 m**
Buyer rent	**€154 m**	Buyer rent	€270 m	€97 m	€50 m	**€417 m**
Cost to public in nominal value	**€283 m**	Cost to public in nominal value	€283 m	€147 m	€109 m	**€539 m**
Cost to public incl. unserved patients	**€441 m**	Cost to public incl. unserved patients	€441 m	€228 m	€170 m	**€839 m**

In the model, based on historic sales data, **the buyer captures 43% of the voucher's value** if there is one voucher per year, and 61% if there are three vouchers annually. The buyer's share is sensitive to the gap in the voucher's value between one buyer and the next. The smaller the gap, the higher proportion of the value remains with the developer (seller). Appropriate safeguards and modulation of the voucher system could potentially improve the buyer/seller value-sharing ratio.

The voucher not only generously rewards the buyer without merits, but the public has to pay a high price to the developer. We present the cost for the public payer to reward the developer with 1€ in **Table 10** both in nominal value (the net budgetary effect for payers) and with a cost that takes into account the lost volumes and thus unserved patients.

Table 10 - cost for the public payer to reward the developer with 1€

Scenario	1 voucher	2 vouchers	3 vouchers
Cost to public in nominal value	**1.38 €**	**1.40 €**	**2.02 €**
Cost to public incl. unserved patients	**2.15 €**	**2.18 €**	**3.14 €**

If it were possible to add safeguards, ensuring that 90% of the value of the voucher is captured by the seller (developer), the ratio of the award and the cost would significantly improve. In this case, it would cost €87 m to the health payers to give a €100 m reward, but this payer cost does not account for the unserved patients' loss[150].

Regardless of the cost calculation method, the public has to pay more than 1€ for each euro awarded to the developer. However, it would be a feasible way **to pool sizeable resources and incentivise antibiotic development,** which so far have proven ineffective with other incentives. These costs should be put on balance with the current **€1.5bn in health care costs and productivity losses from AMR**[151] and the risk from the high levels of antimicrobial resistance in bacteria from human infections, a silent pandemic that is not subsiding, and its economic consequences. Benefits are further detailed in the social impact section (6.2).

In the consultations, some civil society organisations concurred that company profits would rise as a result of a transferable voucher and thus create an incentive to develop products to address the issue of AMR. However, they recognised that if this is done the system should be fine-tuned to meet the needs of patients. Others oppose this incentive as it would delay the entry of generics for other medicines and could increase substantially the costs for public health systems. Alternative solutions such as small milestone rewards or longer regulator protection periods should be considered according to civil society organisations, public authorities, healthcare professionals and citizens. In the public consultation, innovator industry defended the benefits of transferable vouchers. Public authorities, civil society and the generics industry expressed opposing views about the voucher citing arguments linked to overcompensation, high cost to health systems and loss of competitiveness for generics.

Impact of prudent use measures

The use of smaller packages would enable more sustainable use of antimicrobials and less release of unused antimicrobials in the environment. On the opposite side, it would increase manufacturing costs and package waste. Stricter rules on prescription of antimicrobials and mandatory use of diagnostics would impact prescription behaviour positively, however, it would also result in switching from broader spectrum antimicrobials to more specific (and expensive) antimicrobials and costly diagnostic tests. Requirements to adopt AMR lifecycle monitoring plans[152] would help the EU reduce its overall consumption of antimicrobials and hence AMR. This measure would come with some cost both to businesses and Member States, however the establishment of appropriate mechanisms to share information with regulators could mitigate this burden.

6.1.1.5 Horizontal measures[153]

The horizontal measures are intended to deliver wide-ranging improvements in terms of efficiency and effectiveness. **Table 11** presents a qualitative assessment of the benefits of each of the 10 pivotal horizontal measures, rating the likely benefits – against the baseline – on a 3-point scale (High, Medium, Low) for each stakeholder group. From this perspective, the most promising horizontal measures – overall, for all stakeholder groups – are the proposals to improve the governance of the European medicines regulatory network, the development of an integrated, pan-EU data architecture for the regulatory system and an EU-wide, centrally coordinated process for early dialogue.

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[150] Unserved patients refer to those patients that were not served due to the delayed entry of generics, i.e. the lost volume

[151] 201020_EUJAMRAI_policy-brief_WP7_appropriate-use-of-antibiotics-one-health-perspective.pdf (eu-jamrai.eu)

[152] Such AMR lifecycle monitoring plan could cover stewardship, risk mitigation measures to limit AMR, report resistance to the antimicrobial, educational material to inform more efficient use, monitoring and reporting on the use.

[153] Detailed analysis of the measures are in Annex 11.

Table 11 - Qualitative assessment of the benefits of pivotal horizontal measures for key stakeholders

	Business	EMA	NCAs	SMEs	Health Systems	Environ-ment
Streamlining and de-duplication						
#1 Streamlining of procedures	H	M	M	H	L	L
#2 More efficient RUP	H	L	H	L	M	L
#3 Efficient governance of the European Medicines Regulatory Network	H	H	H	H	M	L
#4 Facilitate more efficient interaction across regulatory frameworks	M	H	M	M	M	L
Digitisation						
#5 Legal basis to allow network to analyse real world evidence	M	M	H	H	H	M
#6 Legal basis for setting up electronic product information for medicines	L	M	M	L	M	L
#7 Electronic submission of applications	H	H	M	H	L	L
Enhanced support and regulatory flexibility						
#8 Optimise regulatory support to SMEs and non-commercial organisations	L	M	L	H	H	L
#9 Adaptation of the regulatory system to support the use of new concepts	H	M	M	H	M	L
#10 EU-wide centrally coordinated process for early dialogue	H	M	H	H	M	L

Stakeholders' views are more convergent vis-a-vis horizontal measures. Reducing regulatory burden (e.g. through efficient governance of EMA committees and authorisation procedures, elimination of the renewal procedure and digitisation) can be considered as common ground both for industry and public authorities and improve the competitiveness of the EU as a global destination for businesses.

The introduction of electronic product information is supported by all stakeholder groups. For healthcare professionals and patients it is important to keep paper package leaflets in certain cases to ensure access to information for all patients. Member States want that the different national levels of 'digital readiness' are respected. The electronic product information will complement the current paper package leaflet of authorised, statutory information for each medicine, though in certain cases Member States could allow electronic product information only. It could have positive effects on shortages and will be more appropriate to the EU's multi-lingual environment. The electronic product information will have a limited, positive environmental impact from reducing the number of paper package leaflets and streamlining the logistics chain.

An EU-wide centrally coordinated process for early dialogue among authorities responsible for clinical trials, marketing authorisation, health technology assessment, and pricing and reimbursement will improve business predictability for companies (including SMEs). Such early dialogues are expected to provide guidance to companies on evidence generation along the medicine lifecycle. Clearer and more coherent evidence requirements will reduce uncertainty and investment risks for developers of innovative medicines, in particular in areas of unmet medical need (where developers often already face significant challenges due to the complexity of the diseases concerned). Early dialogues can therefore contribute to guiding and steering the investment and clinical development decisions of companies towards innovations with high added value for health systems and patients. They will also ultimately contribute to timely patient access to innovative medicines by providing clarity on evidence requirements of downstream actors for timely generation of appropriate evidence, facilitating and speeding up their decision-making.

Overall, these measures are expected to generate net benefit of up to €100m a year, shared among businesses and authorities (Annex 3) in the best case scenario.

6.1.2 Option A – combined impact of the measures

Conduct of business: Retention of the current period of RP for all new medicines and special incentives for UMN, comparative trials and EU-wide product launch would have a positive effect on businesses that can benefit from the incentives. However, this would negatively impact the generic and biosimilar industry as it would further delay their access to the market. Measures on security of supply retain the current requirements hence they would bring no additional burden.

Public authorities: Incentives providing longer data protection periods in general (whether to promote innovation or EU-wide market launch) would carry a significant cost to national health systems and payers by delaying generic entry. There would also be additional administrative burden for the EMA and NCAs involved in the assessment of the additional applications, UMN criteria and verification of product market launch information to determine whether a MAH has fulfilled all the conditions to be eligible for longer data protection. On the other hand, a special incentive for comparative trials would offset an additional period of high prices for payers against a more robust evidence base for HTAs and payers.

The high cost of a transferable voucher given to developers of novel antimicrobials would be borne by healthcare payers. This cost needs to be considered in the context of the health costs related to AMR and possible savings from novel antimicrobials to combat resistant bacteria.

Sectoral competitiveness, trade and investment flows: The special incentives for UMN, including the transferable voucher and EU-wide market launch are expected to improve competitiveness and attractiveness of the EU pharmaceutical sector, especially SMEs and support increased investment in medicine development to address UMN and AMR respectively.

Research and innovation: The special incentives will support increased return on investment for developers and bring additional investment into R&D for UMN, including AMR. Comparative trials will contribute to better understanding the clinical benefits of a medicine and its comparators.

Functioning of the internal market: The slight increase in the number of new innovative centrally authorised medicines owing to incentives and the increase in access to those medicines through the market launch incentive will improve the functioning of the internal market. On the other hand, delayed generic entry would hinder competition, and keep prices high for a longer period compared to the baseline. Overall, option A would make more harm to the functioning of the internal market than benefit.

Administrative burden on business: Changes to RP for medicines to make them contingent on market launch should be expected to make the system considerably more complex. It will require reporting by MAHs on market launches resulting in higher administration costs. The horizontal measures however would significantly cut red tape.

SMEs: The transferable exclusivity voucher is intended to reward antibiotic developers that are often SMEs. Thanks to the transferability, they can monetise the value of the voucher by selling it. Fulfilling the conditions for the market launch incentive is more challenging for SMEs compared to big companies that may have offices and staff in all Member States. As mentioned in the 'SME test' Appendix D of Annex 12, other measures in Option A present no major positive or negative impacts.

6.1.3 Option B – combined impact of the measures

Conduct of business**:** For originators affected by the reduced RP, the overall income and profitability from new medicines would be significantly reduced (22% loss in commercial value). It may happen that developers increase their prices or otherwise rebalance their portfolios towards those market segments with greater commercial potential. The threat to EU-based originators will be offset to some degree by giving a boost to EU's generic industries, broadening their portfolios and potentially creating a prime-mover advantage in global markets. Similarly, developers of products addressing UMN will be exempt from the negative impacts of the measure.

A pay or play model would impose additional costs on EU pharmaceutical businesses, and while a minority may look to avoid a levy by developing antimicrobials or acquire businesses with an antimicrobial in their portfolio, the majority would be likely to view the surcharge as an unavoidable additional cost to be factored into their wider pricing policies.

Public authorities: Health payers may benefit from lower average lifetime costs for medicines due to earlier generic entry (because of a reduced data protection period). The extent of these benefits will depend on originators' response to the reduced incentives, and it is possible that average prices will be adjusted upwards to some degree to offset the shortened protection period.

Greater transparency around public support for medicines development may strengthen payers' position when negotiating with MAHs, helping to place a downward pressure on prices and thereby helping to maintain or improve access to medicines. Auditing the claim of developers demonstrating the absence of return on investment can be time consuming for authorities; the global development and the complex accounting systems raise questions on the overall feasibility of the exercise.

The measures to increase patient access to medicines are expected to improve the situation in particular in smaller markets, and thus the cost-effectiveness of the health systems.

Creating the infrastructure and monitoring shortages will require a significant investment from authorities. However, shortages avoided reduce the burden of finding substitutes or new suppliers.

Sectoral competitiveness, trade and investment flows: Reduction in the standard regulatory protection could weaken the global competitiveness of EU based originators overall, compared with the current situation. The reduction will affect equally all companies selling their products in the EU, no matter where their R&D is placed. The proposed pay or play model and access obligation would raise the cost of doing business in EU. This could affect the competitiveness of pharmaceutical companies in EU relative to non-EU companies.

Research and innovation: The reduction of the regulatory protection would cause an estimated annual €670m loss for R&D.

Functioning of the internal market: Earlier generic entry due to lowering of the standard data protection period for most new medicines (except those addressing an UMN) and increase in access to medicines through market launch obligations improve access to medicines and the functioning of the internal market. Reduced number of new innovative medicines would offset parts of the benefit.

Administrative burden on business: For developers that need to demonstrate the absence of a return on investment (ROI) from their R&D to secure a period of additional regulatory protection, there would be increased administrative costs associated with the methodology that businesses would need to follow. The transparency requirements would put an additional burden on companies. The horizontal measures however (discussed in section 8) would significantly cut red tape.

Obligations on MAHs to place centrally authorised medicines on the market in a majority of Member States may carry additional costs to the MAH that would have to bear the consequences of the reduced regulatory protection. The MAH will also have to provide additional information to regulators to demonstrate their compliance with obligations, raising costs. These obligations will also increase the costs to MAHs for interacting with HTA bodies in the Member States.

Administrative costs would also be expected for AMR measures in relation to the pay or play model and prudent use measure, e.g. monitoring of consumption.

SMEs: SME originators may find it more difficult to invest in riskier novel medicines given the reduction in future returns on investment owing to reduction in the standard data protection period and their relatively weaker market position when it comes to negotiating prices. On the other hand SMEs could benefit from the UMN incentive as they are often willing to invest in more risky R&D.

Obligations for market launch in a minimum number of Member States, including smaller markets, may be more challenging to meet for SMEs that do not yet have market presence.

6.1.4 Option C – combined impact of the measures

Conduct of business: Under this option, companies will be able to obtain the same protection period as in the baseline, but subject to compliance with certain conditions on which the eligibility for those "conditional" periods depend. Access to additional incentives for market launch and supply in all Member States, innovation for UMN and AMR as well as comparative trials will grant MAHs a longer period of exclusive prices compared to the minimum period being introduced, representing increased revenue and potentially changing behaviour of the sector. For companies not complying with the criteria for the conditional periods, impacts to conduct of business will be similar to those for Option B with reduction in overall income and profitability for new medicines. In addition, generic companies have the opportunity to enter the market earlier when originators have not fulfilled the RP prolongation conditions.

As regards shortages, submission of shortage prevention plans and additional reporting requirements to increase transparency of the supply chain would be acceptable to industry stakeholders if the information remains confidential, as this could be commercially sensitive. In consultations, industry stakeholders have strongly opposed applying these measures to all authorised medicines rather than limiting it to critical medicines and those medicines at high risk of shortage.

Public authorities: It is a win-win for public authorities, partly because their role in market launch is strengthened and no longer depending on companies only. Either after a successful price or reimbursement negotiation the medicine will become available to patients, or if there is no compliance, the measure will allow earlier market entry of generics and biosimilars thus reducing prices through generic and biosimilar competition. The strengthened role of Member States comes though with increased responsibilities for timely decisions at national level. The special incentive for comparative trials would lead to increased availability of such data to regulators at time of authorisation and may provide a better evidence base for HTAs and payers.

There may be additional costs for the public authorities involved in the assessment of UMN criteria and verification of product market supply to determine whether a MAH is eligible for longer data protection. Similarly, an increase in notification period for withdrawals and shortages will increase the complexity and administrative burden of monitoring shortages for Member States' authorities, although use of a common template and streamlined reporting for reporting could enable cost savings in the long term. Monitoring of supply at Member State level is economically advantageous for NCAs as it builds upon the existing system of national monitoring.

To support market launch of products in Member States, HTA, pricing and reimbursement bodies would have to conduct a greater number of procedures, in a reduced time period. It is observed that national pricing and reimbursement decisions for new medicines often take longer than the legally maximum of 180 days.[154] This can be partly offset by the efficiencies in the new HTA regulation, in particular better sharing of evidence on the therapeutic benefits of the treatment. Greater transparency around public support for clinical trials would strengthen pricing and reimbursement agencies' negotiating position with MAHs.

Member States would have new burden from supplying marketing authorisation holders with confirmations, refusals or waivers on the compliance with conditions for market launch extension. For AMR, public authorities would need extra capacity to assess AMR lifecycle monitoring plans.

The EMA and NCAs may require additional capacity and expertise or incur greater administrative burden in reviewing and assessing products based on the additional requirements for ERA and GMP (AMR aspects).

Sectoral competitiveness, trade and investment flows: By providing additional incentives (UMN, AMR, comparative trial) companies could get the same regulatory protection period as in the

[154] The Directive 89/105/CEE sets a maximum period of 180 days. For compliance issues see e.g. SWD(2012) 29 final.

baseline (8+2), and the EU pharmaceutical sector would remain attractive. In recent years, global venture capital investment has seen accelerating growth driven by advances in drug research and residual unmet need for which it is often easier to demonstrate value to patients/the healthcare systems[155]. The conditional EU-wide market launch incentive would apply to both EU and non-EU based companies, therefore the relative competitiveness of EU companies would not be driven down. The greater obligations and requirements to monitor and prevent shortages (including reporting and stockpiling requirements) and to address environmental challenges could affect more the EU pharmaceutical sector, but these measures are proportionate to achieving the objectives of security of supply of medicines at all times and reducing the environmental impact of pharmaceuticals. The overall balance of the measures on competitiveness would still be positive.

Research and innovation: Impacts on research and innovation would be similar to Option A.

Functioning of the internal market: The increase in the number of new innovative medicines owing to incentives and the increase in access across the EU through the market launch incentive will improve patient coverage and functioning of the internal market. Transferable vouchers would delay the start date of competition for the product to which the voucher is transferred, but the systemic impact would be limited due to the low number of vouchers and products benefiting from them.

Administrative burden on business: Additional regulatory data protection period for medicines contingent on appropriate and continuous supply will require MAHs to seek confirmation of supply from Member States resulting in higher administration costs. Similarly, an increase in notification period for withdrawals (12 months) and shortages (6 months) will increase the administrative burden of reporting shortages for MAHs. Introduction of a common template for reporting withdrawals and shortages could help reduce the additional administrative burden and promote harmonised data collection. Keeping monitoring at Member State level will not lead to additional burden for MAHs as it builds upon existing systems. MAHs will also incur greater costs due to requirements for stockpiling and shortage prevention and mitigation plans for all medicines. The horizontal measures however (see section 8) would significantly cut red tape.

Increased transparency around public support for clinical trials is narrower than the proposal under Option B, where all aspects of public support for medicines development, including various tax reliefs, have to be considered. Hence, this option would be simpler to implement as information on support of specific clinical trials through publicly funded R&D grants is more easy to retrieve and thus will incur less substantial administrative costs.

For AMR, prudent use measures would increase the administrative burden for businesses, e.g. for AMR lifecycle monitoring plans. Strengthened ERA would also increase the administrative burden for businesses.

SMEs: There may be additional administrative burden on SMEs to meet the strengthened requirements for ERA. The greatly expanded obligations and requirements for withdrawal/shortage reporting and management would also put a relatively larger burden on SMEs compared to their larger counterparts. On the other hand, SMEs should benefit from the introduction of regulatory sandboxes to support development of innovative products and scientific support from the Agency, as well as fee reductions. Incentives for UMN and AMR are also expected to benefit more SMEs, including biopharmaceutical companies, as they are more active in risky early-stage drug discovery.

6.2 Social impacts

Public health and safety is the key impact assessed under the social dimension of the legislation and includes patients' and health system interests.

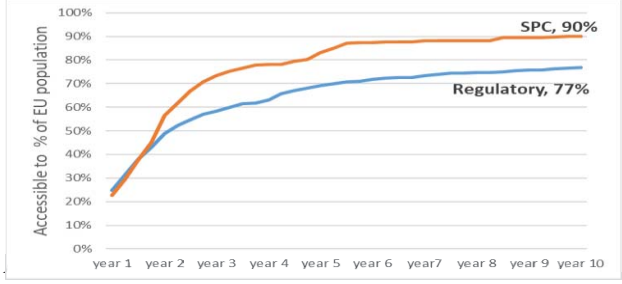


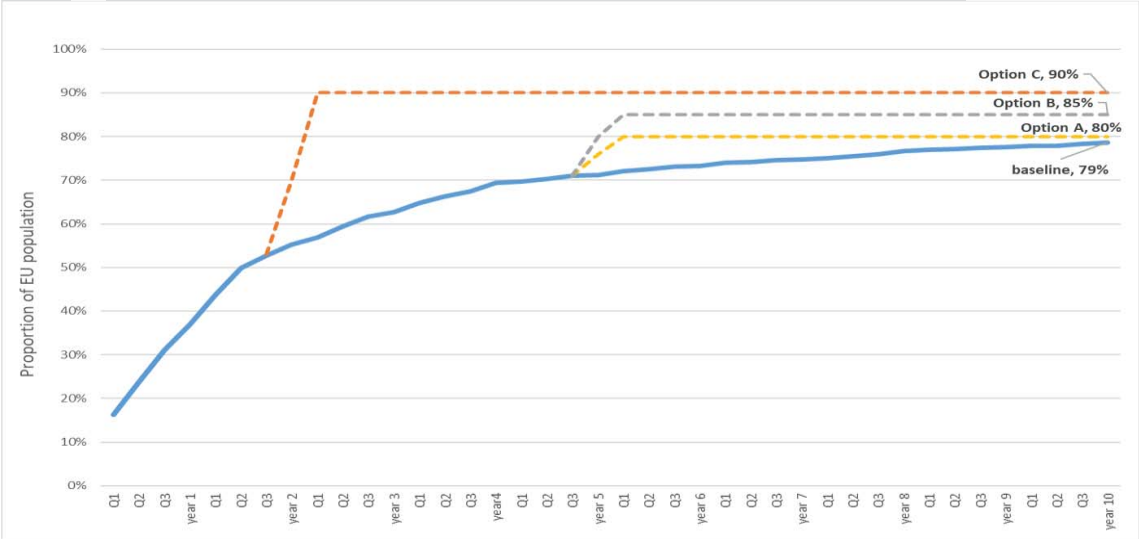
Figure 8 Avg product accessibility to EU population

[155] The financial ecosystem of pharmaceutical R&D: https://www.rijksoverheid.nl/documenten/rapporten/2022/02/28/tl

Among the specific objectives of this revision, the one on **access** is directly impacting patients. Analysis of historical data[156] reveals that access to newly authorised medicines in the EU is unequal and there is a large variation in time to access. Moreover, medicines whose last layer of protection is SPC are more accessible than RP protected ones (**Figure 8**).

All policy options seek to address this objective, using either incentives or reducing protection in case of non-compliance. **Figure 9** shows the likely social impact of the various options. We compared the options to the baseline in terms of time to access and proportion of EU population gaining access to a model RP protected medicine.

Figure 9 Proportion of EU population gaining access over time in various options



Based on the assumed compliance rate (Option A – 50%, Option B – 75%[157], Option C - 66%) and time limits to comply, we modelled when and what percentage of the EU population can gain access to the average RP protected medicine (see also section 6.1.1.3).

Option C outperforms all options, by providing access on average to 80% of EU population over the 10 years protected period, 15% higher than in the baseline (65.3%). Also options A and B offer a higher access than the baseline (67.6% and 70.2% respectively). In other words, in Option A 11 million, in Option B 22 million and in Option C 67 million more EU citizens would have access to a typical RP protected medicinal product, should they need it[158] compared to the baseline.

The special incentives under Options A and C should support increased R&D investment, especially in areas of UMN and this should flow through to an increase in treatment options and benefit more patients. Comparative trials will provide a better evidence base for reimbursement decisions, potentially leading to cost-effective medicines becoming more readily available to those that need them. Such trials also tend to assess patient relevant parameters, such as their quality of life and provide better information to healthcare providers for evidence based treatment decisions.

The reduced regulatory protection in Option B would allow earlier generic/biosimilar entry, lower prices and eventually increase the number of patients treated with the concerned medicines. The positive impacts would be somewhat offset by reduced innovation, and the delayed or no entry of some innovative products to the EU market.

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[156] See Annex 4 (analytical methods and methodology) and Annex 5 (evaluation SWD).
[157] Not all, but for majority of markets.
[158] The medicines that were modelled with the average medicine, can be manifold in fact. They may address a small or big patient population, can offer higher or lower therapeutic value, therefore we refrained from converting the coverage rate into QALYs or other similar indicator that could thus compromise the integrity of the analysis.

The transferable exclusivity voucher in Option A and C would help develop novel antibiotics. While the scheme would apply to a limited number of novel antibiotics which need to be used selectively, i.e. as a last-line therapeutic option (to avoid bacteria developing resistance against them), they serve as an 'insurance' scheme for the EU and global population. The growing threat of antimicrobial resistance means that routine hospital procedures such as a hip replacement or a caesarean section can turn fatal. So far, these events are sporadic within the EU, but can develop into a dangerous public health emergency in the future. Novel antibiotics on the shelf can protect citizens from such a crisis and the health and economic cost of AMR in case of inaction may be much higher. Moreover, strict conditions for defining a 'novel' antibiotics will help to ensure that this incentive is not just a windfall profit for products already in the (weak) pipeline, but encourage additional investment in research.

In the public consultation, stakeholders rate access to medicines in the EU as ‘moderate’ or ‘poor’ (64.1%). The favoured policy responses differ between respondents; industry placing the root causes as factors outside the control of the legislation, and public authorities and patients advocating for obligations or conditions as incentives for access or stronger notification requirements (e.g. for shortages and withdrawals). For AMR, the highest ranking measure to address AMR was introduction of a ‘pay or play’ model (Option B) mostly supported by civil society organisations and opposed by the industry which supported additional market protection period for novel antimicrobials and the transferable exclusivity voucher.

6.3 Environmental impact

To address the issue of pharmaceutical residues in the environment, and in drinking and natural waters, different measures have been considered under the policy options. The general pharmaceutical legislation addresses the impact of pharmaceuticals in the environment through requirements for an environmental risk assessment (ERA) and related conditions of use and mitigation measures along the lifecycle of medicines. These measures complement those under the environmental policy and legislation to reduce the environmental impact of medicines; several specific environmental legal acts are under review, see section 1.1.

A common measure across all policy options is the more prudent prescription rules for antimicrobials, which should result in fewer antibiotics entering the environment.

For Option A, the current **ERA requirements** continue with an additional obligation to include the information on the environmental impact of the supply chain in the application dossier. The impact of Option A would not be very different to the baseline, though a greater environmental awareness of the supply chain actors could be envisaged.

Option B increases the requirements for ERA, by including the assessment of the environmental risk of manufacturing as part of the marketing authorisation process. Option C would in addition strengthen the conditions of use of medicines and include AMR aspects in GMP to allow a more holistic assessment of environmental risk along the pharmaceutical lifecycle.[159]

The overall impact of options B and C should be less residues (e.g. genotoxic substances, antimicrobials) in the environment and less disruptions to the ecosystem and human health. Strengthening the ERA in the general pharmaceutical legislation is expected to have a positive effect by increasing environmental awareness and responsibilities in the pharmaceutical sector. Furthermore, a strengthened ERA will also provide an improved basis for taking environmental risk minimisation measures, enhanced obligations for ERA updates, monitoring of medicines use and conditions for prudent use. Enforcement should be strengthened as well. The inclusion of assessment of environmental risk of manufacturing in the ERA would allow tracking the environmental risks of manufacturing across the supply chain providing a more comprehensive assessment of the potential

[159] Annex 11 describes the assessment of the proposed measures (tables 47 and 64) in qualitative terms.

environmental impact of a new medicine, but the measure could result in high costs and administrative burden and pharmaceutical inspectors may not have expertise to check compliance.

For option C, inclusion of AMR aspects into GMP would help minimise amounts of antibiotics entering the environment via manufacturing and thus prevent or reduce emergence of AMR from manufacturing of medicines. Companies would have additional costs to comply with AMR requirements in GMP and public authorities would have additional enforcement costs.

Some limited positive environmental impacts are expected from digitalisation such as electronic package leaflet and electronic submission of applications in terms of reduced use of paper and streamlining of the logistics chain.

In the consultations, stakeholders have pointed out that the introduction of new rules at an EU level has been known to be a trigger for other regions, leveraging on EU actions. There is variable stakeholder support on strengthening the ERA which ranges from support for it to cover all stages of pharmaceutical lifecycle, from raw materials to end-product (public authorities and citizens) to views considering existing measures (controls, benchmarking on the manufacturing and disposal of products in the environment) stringent enough (industry). According to the targeted survey (Annex 2), the inclusion of assessment of environmental risk of manufacturing in the ERA was mostly negatively rated by industry while all other stakeholder groups viewed this option as bringing a positive impact. A workshop conducted for this IA confirmed the general view that there is a tension between reducing regulatory burden while expanding environmental obligations.

The policy options are aligned with the EU climate-neutrality objective and consistent with ensuring progress on adaption to climate change. The policy options aim at reducing medicine residues in the environment and thereby reducing the environmental footprint.

7 HOW DO THE OPTIONS COMPARE?

This section compares the expected impacts of the options in relation to the baseline in terms of their effectiveness, efficiency, coherence, EU-added value, proportionality and subsidiarity.

The comparison focusses on the pivotal elements as these have the most significant impacts and will allow clear differentiation between the options. The horizontal measures together with the pivotal elements respond to the objective of **innovation and** will impact on the objective of reducing regulatory burden and providing a flexible regulatory framework. The other objectives are mainly impacted by the pivotal elements alone. The overall comparison of the options against the relevant criteria is presented in **Table 12**. The complete analysis of all the elements is provided in Annex 11.

Table 12 Overall comparison of policy options

Criteria	Baseline	Policy Option A	Policy Option B	Policy Option C
Effectiveness: contributing to achieving the policy objectives				
Promote innovation,	0	++	-	+
in particular for unmet medical needs	0	+++	0	+++
Create a balanced system for pharmaceuticals in the EU that promotes affordability for health systems while rewarding innovation	0	--	++	+
Ensure access to innovative and established medicines for patients with special attention to enhancing security of supply across the EU	0	+	++	+++
Reduce environmental impact of the pharmaceutical product lifecycle	0	+	++	+++
Reduce regulatory burden and provide a flexible regulatory framework	0	+++	++	++
Effectiveness: other impacts				
Competitiveness, SME, single markets	0	+	+	++
Social impacts (patients, public health and safety)	0	++	+	+++
Environmental impacts	0	+	++	+++

Criteria	Baseline	Policy Option A	Policy Option B	Policy Option C
Efficiency				
Administrative and compliance costs	0	++	++	+
Savings and benefits	0	+	++	+++
Coherence	0	+	++	++
EU added value	0	++	++	+++
Proportionality and subsidiarity	0	+	+	++
Overall	**0**	**+**	**+**	**+++**

For efficiency, effectiveness, coherence and EU added value, the scores are given on the expected magnitude of impact as explained above: + + + being strongly positive, + + positive, + moderately positive, 0 neutral, – moderately negative, – – negative and – – strongly negative.

7.1 Effectiveness

Innovation

Option A offers the same default incentives for innovation as the baseline with some additional ones in particular for UMN and AMR. Overall, Option A is slightly more generous towards innovators, as in this option incentives can be freely cumulated. Option C on the other hand offers lower default incentives for innovation than Option A, however under Option C companies can still get the baseline protection period if they comply with certain conditions (market launch, UMN, comparative trials etc.). In Option C, the maximum period of RP is capped. Option B keeps the baseline protection period for UMN medicines, whereas for other RP protected originator medicines there will be a 15% loss in profits. We estimate that this translates into €670m loss to innovation funding annually. The pay or play model in Option B is considered less effective than the transferable exclusivity voucher of Option A and C in stimulating AMR related innovation. It is important to note that the revision does not affect the incentives pertaining to intellectual property rights (patents and SPCs). These offer IP protection to the invention(s) associated with the medicine and can extend the effective protection period beyond RP. As Figure 3 illustrates, for about half of the medicines on the market, SPC is the protection that expires last. This important incentive for innovation would still be available for most of the products on the market despite a modulation of regulatory incentives. The revised SPC regime will not change the duration, but streamlines the way an SPC can be obtained through a single granting mechanism or a unitary SPC and ensuring legal certainty for innovative companies.

Horizontal measures will facilitate the secondary use of health data, including real-world evidence, for innovators (including SMEs and academia), and for regulatory decision-making. Wider and more systematic access to real world evidence will be integrated in the lifecycle of a medicine, from early stage of development (complementarity with clinical trials data), to authorisation and post-marketing supervision. In this context, the European Health Data Space infrastructure will provide a significant positive economic impact of at least €5.4bn over the next 10 years, stemming from efficiency gains as a results of a less costly access to health data by reusers (€3.4bn), greater information transparency for policy-makers and regulators (€0.8bn), and increased value for patients, healthcare providers and innovators thanks to further reuse of health data[160]. The complementarity of this initiative with the European Health Data Space, via the facilitation of the secondary use of health data, will have a direct benefit for all pharmaceutical companies, including SMEs.

Option C combined with horizontal elements, especially simplification, regulatory flexibilities and digitalisation is more beneficial to innovation compared to the baseline.

[160] COM SWD(2022) 131 final https://data.consilium.europa.eu/doc/document/ST-8751-2022-ADD-3/en/pdf

Affordability

In terms of affordability, the general pharmaceutical legislation has a limited role to play, as pricing and reimbursement of medicines is a Member State prerogative. Nevertheless, the regulatory protection has an impact on affordability, as it delays generic competition and keeps prices higher. As demonstrated in section 6.1, two-thirds of the medicines are protected from generic competition thanks to their SPC or patent protection, therefore any change to the RP would have no effect on them. According to the draft impact assessment on the revision of the SPC legislation, the unitary SPC system would not significantly affect the entry of generics and biosimilars on less attractive (smaller or peripheral) markets in the EU; the larger and more central EU markets usually remain unaffected as SPCs are sought there anyway. This is possibly so as other factors play a far more important role in a decision to enter a market, such as: pricing and reimbursement rules, legal uncertainty connected to the country, quality and readiness of healthcare systems, differences in the value assessment process, overall levels of pharmaceutical spending and size of the market. The additional annual expenditure on medicines that might be a result of wider territorial SPC coverage due to the unitary SPC is estimated at €37m.[161]

With these limitations, Option B offers the most effective measure in terms of affordability, offering €1.13bn direct cost reduction for health payers with the reduced RP period (6+2 years). This reduction of 0.5%-0.6% of the EU pharmaceutical expenditure would heavily impact 20-25%[162] of the new medicines (they would lose 15% of their gross profits) while other, often more profitable, medicines would be unaffected. Option A keeps the baseline protection period. The R&D transparency requirements in option B and C are supposed to indirectly contribute to affordability too, better equipping with additional evidence national bodies for price negotiations.

The market launch in option B is an obligation with no additional period of protection whereas in option C market launch is linked to an incentive. In both cases, if the market launch does not take place, it would at least result in cost savings to the public as non-complying medicines would lose a part of their protection period resulting in an earlier entry of generics or biosimilars. In option A, the market launch incentive would come with an extra €455m cost to the public. Options A and C offer additional incentives for UMN, and for the transferable exclusivity voucher, which come with additional costs. This is a **trade-off between innovation and affordability.** Options A and C also offer an incentive for comparative trials, however the cost of that incentive is counterbalanced by savings to the health systems by more informed pricing and reimbursement decisions, with an expected overall neutral/positive impact on affordability. However, this could not be quantified.

Options B and C include an expansion of the so-called Bolar provision to facilitate market entry of generic and biosimilar medicines immediately after the expiry of regulatory or intellectual property right protection periods. Market entry of these medicines lower generally the price of the innovator product and are themselves cheaper[163] and thus make savings for the healthcare systems, e.g. in 2020, the list price savings (excluding confidential rebates and discounts) accounted for €5.7bn in savings from biosimilar medicine versus the pre-biosimilar cost of the originator[164].

Option C is the most advantageous by far from a patient/public health perspective, and it represents a fair balance between originator and generic industry, along with public authorities and payers.

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[161] Based on historic data (2010-2021) the country with the most significant estimated impact was Latvia in 2019, where additional spending could reach up to 0.48% of pharmaceutical expenditure, cf. section 6.6.2 of the draft SPC IA.

[162] Those having SPC or patent protection, having an orphan market exclusivity, or having an UMN or no return on investment status in option B would be exempt from the impacts of the decreased RP.

[163] Analytical report, indicator AFF-6, Annex 10.

[164] The Impact of Biosimilar Competition in Europe, December 2021, IQVIA.

Access and shortages

All options result in more and quicker market access of new medicines, compared to the baseline. The least increase is with Option A and that is the costliest measure for the public. Options B and C are not only more effective, but they are synergistic with affordability. In these options, the public wins in either case: more timely access across the EU if companies comply with market launch conditions, or earlier generic competition and affordability if they do not. The gain in access is highest with option C, thanks to the shorter deadline to compliance (2 years) and to the all-EU launch requirement (vs majority of Member States in option B).

Option A does not represent a significant change to the baseline in terms of shortages management, whereas Option B proposes a more coordinated reporting system, and option C even goes beyond that, and also requires earlier notification in case of shortages and withdrawals. As such, Option C has the highest positive impact on shortages, followed by B and A. There is a trade-off among shortages and administrative burden, better and more reporting is needed to address shortages but that comes with a certain administrative cost.

Environment

Option A does not impose additional requirements for the ERA, whereas Option B obliges companies to report about the environmental risks of manufacturing too as part of their MA application. Option C goes further than B, demanding more stringent conditions of use for medicines than the baseline. As with the shortages, there is a trade-off among environment protecting measures and administrative burden.

Regarding the impact on AMR, Option C offers the highest safeguards against the impacts of the release of antimicrobials into the environment, followed by option B, and with no impact for option A. All options feature prudent antibiotic use measures, to reduce antibiotics in the environment, and lower the risk of AMR. Options A and C are also the most effective in financing Europe's 'fair share' of the cost for novel antimicrobial development through a transferable exclusivity voucher while in Option B the 'pay or play' model would not directly increase the number of novel antimicrobials and may risk increasing prices in a broad range of medicines without resulting necessarily in the development of novel antimicrobials (while for the voucher this would concern only the product on which the voucher would be applied).

Regulatory burden and providing a flexible regulatory framework

Horizontal measures feature uniformly across the options, and they will represent a very significant burden reduction for companies and public authorities, through streamlining of procedures, digitisation, enhanced support and regulatory flexibility. In terms of regulatory burden, the difference among the options is restricted to the increased requirements due to more stringent shortages and environmental measures, where options C and B score worse than option A. However, this difference compared to the positive impacts from the horizontal measures is minor.

Impacts on competitiveness and SMEs

In terms of effect on **competitiveness**, the proposed incentives do not make a geographic distinction, they equally offer regulatory protection for products developed in the EU, or anywhere in the world which ensures a level playing field between EU-based and third country-based companies. While the EU regulatory framework is attractive for developers, competitiveness also depends on many other factors e.g. tax system and incentives; available grants, loans and other funding (e.g. the European Innovation Council Accelerator); pool of talents; proximity of top academia; clinical trials infrastructures; market size; security of supply chains; favourable reimbursement decisions.

The horizontal measures described in section 5.2.5 (e.g. simplification, digitalisation, elimination of duplications) and those pertaining to innovation and the futureproofing of the legislation (e.g. flexibility of the framework, clarification of scope, sandboxes, codification of rolling reviews and PRIME) are applicable to all options. They are set to enhance the attractiveness of the EU framework globally. In this context, other policies and initiatives working in synergy with this

revision, like the R&I policy, industrial strategy, the EU system of intellectual property rights (patents and supplementary protection periods), the creation of the European Health Data Space, are key factors to promote innovation and EU competitiveness.

In terms of **effects on SMEs,** Option A emphasises support for innovation, but otherwise presents no major positive or negative impacts for SMEs specifically. Option B includes several measures that are expected to negatively impact SMEs disproportionately. In terms of innovation, SME originators may find it more difficult to invest in riskier novel medicines given the reduction in the standard data protection period and their relatively weaker market position when it comes to negotiating prices. In terms of obligations for market placement in a minimum number of MSs, including smaller markets, may be more challenging to meet for SMEs that do not yet have market presence or distribution channels in such markets. The proposed measures in Option C would be the same for big pharma and SMEs, however some of the measures may have greater impact on SMEs, e.g. due to their limited ability to absorb such a reduction in market protection. Mitigating measures such as longer timeframes to comply with requirements for market launch for example would eliminate any disproportionate burden on SMEs. Regulatory sandboxes and the transferable exclusivity voucher for novel antibiotics could be especially beneficial to SMEs because they are more active in innovative fields than big pharma. Similarly, incentives for UMN would benefit SMEs, which are generally willing to make early-stage investments in areas of high risk, by giving more value to their assets even if they are acquired by big pharma in late-stage development. SMEs already enjoy fee exemptions and reductions for regulatory procedures and through the new horizontal measures SMEs will benefit from optimised scientific support with a greater likelihood of success for authorisation. Overall, with the increasing investment in biopharmaceutical R&D and the increasing share of SMEs among developers, biopharma SMEs in the EU and elsewhere would have excellent prospects for the future.

Overall, Option C scores the highest in the multi-criteria analysis, this option addresses the most effectively the specific objectives of the revision, and has the most positive economic, social and environmental impacts.

7.2 Efficiency analysis

This section compares the cost-effectiveness of the policy measures in the different options, based on the models and calculations in section 6. The data in tables are always compared to the baseline. The measures tackling access and affordability (changes in the regulatory protection period) and the incentives for UNM and AMR are the ones expected to have the most substantive economic impacts on the various stakeholders. Tables 13a, 13b and 13c compare the options with all relevant measures (the cost-benefit analysis of the variation to option C is presented in section 8.1).

Table 13a Cost-benefit table of key measures in **Option A**

Option A	Cost/benefit for public payer and patients	Cost/benefit for originators	Cost/benefit for generic industry
+1 year extension of RP for medicines addressing **UMN**	+ €246m cost + 1-2 new UMN addressing medicines	+ €282 gross profit (3 incentives)	- €39m gross profit
+6 months extension of RP for conducting **comparative clinical trials**	+ €328m cost + faster access and cost saving thanks to improved reimbursement decisions	+ €378m gross profit +€280m cost (8 medicines)	- €52m gross profit
+6 months extension of RP for all EU **market launch**	+€455 m public cost +3% access	+€527 m gross profit (7 complying medicines)	- €71m gross profit
Transferable exclusivity voucher	+€441m cost + 1 novel antibiotic	+€387m gross profit (1 voucher)	- €54m gross profit
Total balance	**+ €1.470m cost** + 1-2 new UMN medicines +comparative data +3% access +1 novel antibiotic	**+€1.294m gross profit**	**- €216m gross profit**

Table 13b Cost-benefit table of key measures in **Option B**

Option B	Cost/benefit for public payer and patients	Cost/benefit for originators	Cost/benefit for generic industry
2 year **reduction of RP** (except for UMN)	+€1860m gain innovation loss	**-€1.970m gross profit** (9-12 medicines)	+€266m gross profit
Loss of RP, if no **market launch** in majority of EU within 5 years	+€681m gain +5% access	**-€842m gross profit** (4 non-complying medicines)	+€101m gross profit
Total balance	**+ €2.541m gain** +5% access innovation loss	**- €2.812m gross profit**	**+€367m gross profit**

Table 13c Cost-benefit table of key measures in **Option C**

Option C	Cost/benefit for public payer and patients	Cost/benefit for originators	Cost/benefit for generic industry
2 year conditional protection for **all EU launch in 2 years**	€444 m gain +15% access	-€469m gross profit (5 non-complying MP)	+€63m gross profit
+1 year extension of RP for medicines addressing **UMN**	+ €246m cost + 1-2 new UMN addressing medicines	+ €282m gross profit (3 incentives)	- €39m gross profit
+6 months extension of RP for conducting **comparative clinical trials**	+ €328m cost + faster access and cost saving thanks to improved reimbursement decisions	+ €378m gross profit +€280m cost (8 medicines)	- €52m gross profit
Transferable exclusivity voucher	+€441m cost + 1 novel antibiotic	+€387m gross profit (1 voucher)	- €54m gross profit
Total balance	**+ €571m cost** + 1-2 new UMN medicines +comparative clinical data +15% access +1 novel antibiotic	**+€298m gross profit**	**- €82m gross profit**

The tables provide an overview of the costs and benefits of the different options and on different stakeholder groups. Whenever it was possible, we presented the cost/benefits in a monetised form, however for certain social benefits putting a monetary value was either not possible or not appropriate. Therefore the societal benefits of new UMN addressing medicines, of improved access, of new innovative antibiotics and of comparative clinical data of new medicines are only mentioned in the table, without a monetary value.

In terms of efficiency, option A delivers quite well on all targets and creates the desired societal benefits, however at a significant cost for the public, missing the affordability target. Option B on the other hand is very cost-efficient for patients and public payers, offering altogether €2.5bn savings to the public, around 1% of the annual pharma expenditure. Option B does improve patient access and UMN medicines would receive a relatively higher support (though unchanged compared to baseline). The savings to the public would be borne mostly by the originator industry.

Option C distributes the cost of the additional societal benefits more evenly among the stakeholders, and also effectively delivers on all objectives. In terms of efficiency, option C offers the most cost-effective mix of policy measures. The variation to option C (presented in section 8.1) equally delivers on all objectives in a cost-efficient manner, with a slightly different distribution of cost to offer more gains for public payers and patients.

Horizontal and other measures

In Annex 3, the analysis concluded that the horizontal measures are – in the best case scenario – expected to generate up to around **€300m savings annually regardless of the selected option**, shared among businesses (one-third) and authorities (two-thirds). Additional administrative costs resulting from measures on shortages and environment would offset as a minimum 10% of these savings (min. €30m additional cost) for businesses; likewise for administrations.

Option C offers the most cost-effective solution to achieve the specific objectives, followed by Options B and A.

7.3 Coherence

Options B and C are consistent with the EU Strategic approach to pharmaceuticals in the environment and complementary to the ongoing revisions of the environmental legislation mentioned in section 1.1. All policy options are coherent with the EU Action Plan on Antimicrobial Resistance[165]**.** All three options contribute to SDG 3 ("health and well-being), SDG 9 ("innovation and infrastructure") and SDG 10 ("reduced inequalities") [166] (section 1).

The objective of patient access to affordable medicines is coherent with the objective of the HTA Regulation on timely patient access. Option C with its incentives for both EU-wide access and comparative clinical trials provides the best alignment followed by Option A.

Through the horizontal measures all options will ensure coherence with the sectorial legislations medicines for rare diseases and for children, EMA fees legislation and with EU legal frameworks on medical devices/in vitro diagnostic and on BTC through efficient interaction and synergies between these regulatory frameworks. In addition, options B and C will create more clarity on the interplay between these legal frameworks through the proposed changes in definitions and classification advice. More details available in Annex 6 with regard to medicines for rare diseased and children and in Annex 9 for BTC.

The access related measures in Option C such as the modulation of incentives or the additional obligations of supply will not only have a positive effect on access but also a systemic effect on public and private actors' behaviour, as explained in section 6. At the same time, the European Health Data Space will provide actors access to harmonised EU health data which unlocks possibilities and efficiencies along the pharmaceutical lifecycle in the development of medicines promoting innovation, in the monitoring of medicines for both regulators and marketing authorisation holders and in evidence generation for downstream decisions after marketing authorisation.

The revision of the general pharmaceutical legislation and the revision of the SPC regime with a unitary SPC are coherent in the objectives to promote innovation and reduce regulatory burden. However, the unitary SPC may have a small negative effect on affordability, as mentioned in section 7.1, and a hypothetical risk[167] of delaying generic or biosimilar entry in markets, where the originator has never been present which would have a negative effect on patient access. On the other hand, the predictability for generic/biosimilar companies will increase in the new SPC regime, through a central SPC database, effectively streamlining decision, less risk of litigation and, if litigation occurs, the avoidance of multiple litigation. Together with the measures undertaken under the pharmaceutical revision to support day 1 entry of generics and biosimilars this will facilitate patient access to those products.

HERA would support solutions from the public procurement side to the market failures in the area of antimicrobials. This unprecedented, combination of policy changes is a result of a combined set of actions in related areas (data, procurement, pharmaceuticals) that complement each other and should not be seen in isolation from each other. Together with the futureproofing and simplification elements of this revision they constitute a holistic response which can be expected to radically upgrade the EU's position globally as a place for medicine innovation.

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[165] A European One Health Action Plan against Antimicrobial Resistance (AMR) (June, 2017), available at: https://ec.europa.eu/health/system/files/2020-01/amr_2017_action-plan_0.pdf

[166] Sustainable development in the European Union, overview of progress towards the SDGs in an EU context, 2022 edition, Eurostat (2022)

[167] The risk is considered hypothetical because it is only in very limited cases that generic or biosimilar medicines enter a market where a SPC has not been requested or granted, i.e. a market where the originator has never been present.

7.4 Proportionality and subsidiarity

All three options are consistent with the EU's right to act under the Treaty of the Functioning of the EU (covering public health protection, the single market and the free movement of products within the EU). Moreover, all three options propose actions that will allow the objectives of the revision to be addressed to a greater extent than if Member States were acting alone.

The principle of proportionality is strongly reflected in the discussion of certain trade-offs to be made between the different objectives (section 4). To give an example, trade-offs are inherent between the objective of innovation and affordability often achieved by generic/biosimilar competition. The incentives will remain a key element for innovation but they have to be adapted to better take into account that medicines are not sufficiently accessible by patients in all Member States. This is reflected in Option C which modulates incentives to reward innovation, especially for UMN, but also make the regulatory protection period conditioned to market launch in all Member States. If this condition is not fulfilled generic competition will start earlier, resulting in increased affordability.

With regards to subsidiarity, all options pursue the objectives of the revision and provide a clear demarcation between EU level and Member State level actions. They do not propose any change to the national health care systems which are in the exclusive power of Member States (Article 168 TFEU), but certain measure (e.g. transparency requirements, better evidence base, early dialogue between regulators, HTA bodies and payers) will facilitate decisions of Member States in these areas e.g. pricing and reimbursement.

7.5 Limitations of the comparison

There is a level of potential uncertainty in the findings described in section 7 owing to the influence of other contextual factors such as developments in the pharmaceutical sector, other relevant legislations (e.g. HTA Regulation, Urban Waste Water Directive and SPC Regulation) and policies at Member State level (see for details of factors influencing access to affordable medicines – annex 14). While the influence of external factors has been considered in the design of the options and their analysis there is an unavoidable risk that they may impact or delay some of the expected benefits. Their effects and anticipated unintended consequences (e.g. the effect of some measures on prices of medicines, or the effect of conditionality of certain incentives on innovation) are analysed to the extent possible in section 6. There is also a level of uncertainty owing to the limitations and assumptions involved in assessing and quantifying the likely impacts of the options provided.

All methods applied to our research encountered a varying degree of difficulty in relation to lack of quantitative data available in the databases and sources examined. We did not find enough data to quantify all relevant impacts of every policy measure discussed in the policy options for the future of the legislation. Whenever possible, we have made reasonable assumptions to assess the impacts, but this lack of quantitative data is a key limitation to our analysis.

8 PREFERRED OPTION

The impact assessment indicates that policy option C is most effectively addressing all the objectives of the revision of the general pharmaceutical legislation in an efficient and consistent manner. The measures of option C address in a proportionate manner the underlying problem drives; a mapping of measures against problem drivers can be found in Annex 16.

This option proposes a modulated trade-off between incentivising innovation (for both unmet medical need and antimicrobial resistance) and improving access, R&D transparency, and security of supply of medicines as well as reducing the environmental impact of medicines. The costs and benefits of Option C for different stakeholder types are described below. The below section considers the pivotal measures but also **takes into account the other measures assessed in Annex 11**, along with the impacts of the horizontal measures.

The preferred option conforms to the principles of subsidiarity and proportionality. It respects the national competence on the organisation of the Member States' healthcare systems and provides clear demarcations between EU level and Member State level actions. Given the objectives the revision aims to achieve, the trade-offs and new burdens on companies and authorities are acceptable and proportionate.

It is expected that the revision will not change the current legal instruments, i.e. a Directive and a Regulation, for the general pharmaceutical legislation.

8.1 Costs and benefits of the preferred option

Table 14 reviews the most significant costs and benefits stemming from the pivotal measures, and also includes the variation to Option C described in section 5.2.4. The variation would decrease the 2 year conditional protection to 1 year. As a result, the overall protection level moves down by 1 year for all RP protected medicines, and only 1 year protection remains dependent on the launch condition. The 1 conditional year is a lower "prize" for compliance, thus we assumed that fewer medicines would meet the requirement (50% vs. 66% in the default). The variation allows the legislator to consider the impacts on the various stakeholder groups by "moving the cursor".

Table 14a Cost-benefit table of incentives in Option C (6+2+2) compared to baseline (8+2)

Option C	Cost/benefit for public payer and patients	Cost/benefit for originators	Cost/benefit for generic industry
2 year conditional protection for **all EU launch in 2 years**	€444 m gain +15% access	-€469m gross profit (5 non-complying MP)	+€63m gross profit
+1 year extension of RP for medicines addressing **UMN**	+ €246m cost + 1-2 new UMN addressing medicines	+ €282m gross profit (3 incentives)	- €39m gross profit
+6 months extension of RP for conducting **comparative clinical trials**	+ €328m cost + faster access and cost saving thanks to improved reimbursement decisions	+ €378m gross profit +€280m cost (8 medicines)	- €52m gross profit
Transferable exclusivity voucher	+€441m cost + 1 novel antibiotic	+€387m gross profit (1 voucher)	- €54m gross profit
Total balance	**+ €571m cost** + 1-2 new UMN medicines +comparative clinical data +15% access +1 novel antibiotic	**+€298m gross profit**	**- €82m gross profit**

Table 14b Cost-benefit table of incentives in Option C Variation (6+2+1) compared to baseline (8+2)

Variation to Option C	Cost/benefit for public payer and patients	Cost/benefit for originators	Cost/benefit for generic industry
1 year general reduction of the RP	+€1,008m	-€991m gross profit	+€133m gross profit
1 year conditional protection for **all EU launch in 2 years**	+€384 m gain +8% access	-€378m gross profit (8 non-complying MP)	+€51m gross profit
+1 year extension of RP for medicines addressing **UMN**	+ €246m cost + 1-2 new UMN addressing medicines	+ €282m gross profit (3 incentives)	- €39m gross profit
+6 months extension of RP for conducting **comparative clinical trials**	+ €328m cost + faster access and cost saving thanks to improved reimbursement decisions	+ €378m gross profit +€280m cost (8 medicines)	- €52m gross profit
Transferable exclusivity voucher	+€441m cost + 1 novel antibiotic	+€387m gross profit (1 voucher)	- €54m gross profit
Total balance	**+ €377m gain** + 1-2 new UMN medicines +comparative clinical data +8% access +1 novel antibiotic	**-€602m gross profit**	**+€39m gross profit**

In the default Option C, the higher market access is achieved without extra cost to the public, even some gains could be expected in case of non-complying medicines. The other incentives would mean an extra cost to the public and to generics, nonetheless it is expected that the indirect benefits from the medicines addressing UMN and faster and better reimbursement decisions, would offset

these costs. The originator companies would have additional costs and benefits from the incentives and the market launch conditionality, and overall they would see an increase in their sales.

In the variation of option C the public would gain significantly compared to the baseline in monetary terms and also enjoy the benefits of the measures. The gains would even allow financing the transferable voucher to support development of novel antimicrobials, without turning the public monetary balance into negative. In the variation, all the costs of the positive social impacts would be translated into reduced revenues for innovator companies, though a significant proportion of the costs would come from non-compliance (e.g. not launching in all EU markets, not carrying out comparative trials), which companies should avoid by complying.

In the variation the cost is put only on a subset of innovator companies, e.g. high-sales, SPC protected medicines would be unaffected. The shorter conditional period for market launch (1 instead of 2 years) means a smaller loss of revenue if companies do not launch in all EU markets, therefore a lower compliance rate (50%) is assumed, resulting in smaller positive effect on patient access. The loss to innovators may translate into slightly less innovation.

Option C and its variant are both cost-effective alternatives to reach all the objectives, the slight difference between the two being the different focus on more access or more affordability (+15% access and €571m more cost vs. +8% access and €377m gains) for the public payer and patients.

Patients, Citizens and Healthcare services

Option C will bring **benefits to patients and citizens** by facilitating the work of healthcare professionals, pharmacies, hospitals and strengthening health. The new measures to promote access across all Member States, by incentivising companies to launch their products on all EU markets, coupled with lower revenues for companies in case of non-compliance will be the first EU-level legislative measure to address the long-standing inequalities **and will increase patient access to innovative medicines**. Facilitating the entry of generics and biosimilars will increase affordability and consequently increase the number of patients treated. The additional incentive for addressing UMN will incentivise the development of more medicines with high public health benefit. Transferable vouchers would lead to development of novel antimicrobials, reduce EU deaths and health system costs due to AMR, and ensure a better preparedness against the increasing threat of resistant bacteria. **Security of supply** measures will improve continuous availability of both critical and non-critical medicines, which will significantly reduce shortages of medicines and benefit patients and healthcare services. Citizens will also benefit from measures taken to reduce the impact of pharmaceuticals on the environment and on public health via the environment through a strengthened environmental risk assessment of medicines along their lifecycle and imposition of appropriate measures to mitigate these risks.

Several other measures discussed in Annex 11 will corroborate the impacts of the pivotal measures: Option C would give a push to repurposing of medicines, as a cost-efficient way to expand therapeutic uses of medicines instead of a rather selective and even risky off-label use (C.1.2., C.1.3.)[168]. Along with the measures facilitating generic entry right after protection expiry (C.1.4., C.5.1., C.5.2., C.5.4., C.5.5.), these will further expand patients' access to medicines. Prudent use measures for **antimicrobials** will help decrease the risk of AMR (C.2.3, C.2.4, C.2.5).

A harmonised system for authorisation of medicines in the EU – through the general pharmaceutical legislation – offers clear EU-added value for public health to enable access to and innovation of medicines. In addition, EU-level action is the most efficient mechanism – in the scope of this revision – to address the concerns Member States have raised about unequal access and affordability, in particular for the centrally authorised medicines.

[168] The codes in brackets refer to the codes of the measures in Annex 11for easier identification

Future proofing measures of Option C will ensure patient safety in areas of rapid technological change, including personalised medicine. Currently, Directive 2001/83/EC covers all 'medicinal products' that are "either prepared industrially or that are manufactured by a method involving an industrial process". "Delinking" the legislation's scope from the way medicines are manufactured will address potential regulatory gaps (without changing the overall scope) due to scientific and technological developments e.g. low-volume products, bedside-manufactured or single batch personalised medicines that do not involve an industrial manufacturing process[169] (C.3.3.). Adapted regulatory pathways, e.g. for less complex cell-based medicinal products, and regulatory sandboxes will also increase the chance of faster patient access to cutting edge medicinal products (C.3.5., C.3.6.). Lastly, allowing electronic product information will bring advances to readability for patients and opportunities for healthcare professionals to communicate information more effectively (Horizontal 6).

Industry

For the originator industry, the modulation of the regulatory protection means a lower standard **duration of regulatory protection**, but companies can achieve a similar/same (depending on the variant in this option) protection as of today if they comply with the **condition to launch in all EU-markets.** The extra condition would entail some additional administrative cost, but that would be somewhat compensated by burden reduction, such as allowing multi-country packs for certain types of medicines (C.4.2.). The special incentive for addressing UMN would offer a longer period of protected sales and thus a higher return on investment, a €282m additional gross profit at industry level. The special incentive for comparative trials will recompense the additional costs from carrying out the trials, and the data will help faster pricing and reimbursement decisions, and earlier market entry. It comes with €378m extra gross profit, but also with €280m cost. The trial data would allow better negotiating position for payers, which may limit company's profits. The transferable exclusivity voucher would reward developers of novel antibiotics, and also the buyers of the vouchers would have gains.

The incentives involving extension of data protection would delay generic entry and keep generic companies out of the market for longer. In the case of UMN incentive of an additional 1 year to originators, it represents a loss of €39m in gross profit per year for generic companies, and €52m for comparative trials. They would also have increased costs from the obligation to include smaller markets in their own mutual recognition procedure (or decentralised procedure) applications (C.1.5, C.1.6.). On the other hand, there should be an increase in R&D activity for generic/biosimilar medicines with a streamlined and clearer regulatory pathway (C.5.1.) and by measures facilitating generic entry right after protection expiry.

Option C also brings greater certainty for businesses by adding clarity and predictability to the regulatory system and the legal pathway (see references to "delinking" in the previous section, as well as adaptation of definitions), streamline the GMO assessment in the authorisation of clinical trials that involve investigational medicines with a GMO component (C.3.2.). These measures should promote **innovation** and attract investment to the EU. SMEs should also benefit from the introduction of regulatory sandboxes to support development of innovative products (C.3.6.) and enhanced support in addition to the current fee reductions.

The preferred option continues to provide a favourable incentive structure for innovation in the EU which remains competitive against what other regions offer. The incentives apply equally to all products, regardless of where they are developed – in the EU or elsewhere; in this regard, the EU competitiveness is not negatively impacted by this option.

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[169] Organised in close coordination with other EU legal frameworks (medical devices, substances of human origin) to avoid shifts of therapies that are already regulated

Greater use of multi-country packs is also expected to facilitate the movement of medicines within the EU internal market, which will help all businesses. In terms of **security of supply**, option C introduces several obligations and requirements on MAHs and wholesalers that likely will carry additional costs to these parties including costs associated with warehousing (for stockpiling), operations and capital (C.6.1. to C.6.9.). Stakeholder consultations estimated that increasing warehouse capacity to accommodate 10% additional stock will have a cost of €500k – 1m per warehouse. This policy option will also require more **transparency** and at the same time obligations regarding supply chain actors and environmental risk assessments, which will result in additional costs for businesses for inspections, compliance and other additional responsibilities. This will likely represent a substantial burden on SMEs in particular.

The horizontal measures on the other hand simplify the regulatory system and reduce burden on industry, reducing compliance costs and administrative burden in the range of €80-160m per year.

For industry, a harmonised and predictable medicines regulatory framework – through the general pharmaceutical legislation – offers clear EU-added value by reducing duplication, simplifying requirements and making the system easier to navigate. The preferred option aims at harmonising requirement concerning shortages.

Despite the new obligations for companies, the preferred option is proportionate when balanced with the efficiency gains, including those from secondary use of health data via the European Health Data Space (see section 7.1), and simplifications introduced and the recognition that other objectives such as patient access and the wider policy ambitions on strategic autonomy and green deal have to be factored in.

Competitiveness and future of innovation under reduced regulatory data protection

Industry stakeholders frequently claim that the reduction of regulatory data protection period would harm future innovation and EU competitiveness. In section 6.1.1.2 we demonstrated that the incentives are agnostic to the geographic origin of the medicines, therefore the reduction would not harm EU companies more than non-EU companies coming to the European market (non-EU companies develop 80% of new medicines introduced to the EU market).

However, lower profits may transform into less innovation at a global scale. Option C results in a slight gain in gross profits but the variation of option C estimates a total loss of €602m in gross profits. Industry re-invests on average 25% of their gross profit into R&D, consequently €150m may be lost for innovation. In 2021 the global pharmaceutical industry has invested €230b in R&D[170], hence the potential loss amounts to 0.07% of global R&D investment. If we wanted to translate this to medicines, only 1 in the next 1500 new medicines would not be developed because of the reduction, a likely invisible loss over the next 15 years.

Public authorities, agencies and payers

Incentives involving additional data protection periods will lengthen the period in which health systems can be charged higher prices for medicines. For example, transferable vouchers would have indirect healthcare costs for the healthcare payer.

Public authorities will require additional budget and expertise for reviewing MA applications (larger number of applications, change in ERA requirements, etc.), enforcement of obligations (e.g. for market launch, lifecycle management of antimicrobials), inspections of manufacturing sites, increased commitments to provide advice (e.g. on interchangeability of biosimilar medicines, ERA, green manufacturing, classification of borderline products etc.) as well as setting up of new centralised infrastructure for information exchange (e.g. for shortage monitoring; one-off costs). Additional costs for EMA in assessing the application for new antimicrobials and the associated

[170] $238b - EvaluatePharma - World Preview 2022, Outlook to 2028, page 20

voucher are estimated at €2m per year. The workload of pricing and reimbursement agencies would also increase with incentives for market launch driving up the number of applications, while their workload should decrease from better evidence provided from more comparative trials.

Health payers would also benefit from measures to promote post-authorisation studies and comparative trials, which would enable access to evidence that supports pricing and reimbursement decisions for HTA bodies. Rejecting immature marketing authorisation applications at time of validation would reduce workload of medicine regulators (C.9.1.) with estimated savings for the EMA and NCAs at 3% of annual costs.

Measures to improve security of supply will facilitate information exchange between Member State authorities and improve strategies to tackle shortages. Both aspects should reduce long-term costs to authorities. However, public authorities will also need to increase capacity to assess shortage prevention plans provided by MAHs, and, depending on the cost and risk-sharing agreements for reserve stock, authorities may also incur direct costs for storage. While measures to improve quality, manufacturing and environmental impact of pharmaceuticals will increase workload for EMA and NCAs, increased coordination, joint audits and data sharing could also result in efficiencies.

Academic/research institutions

Option C will bring benefits for clinical researchers and academics in the form of opportunities to be more involved in the development work and trials, as a binding system for scientific assessment of evidence for repurposing off-patent medicines will be established (C.1.2), and obligations will be simplified to facilitate non-commercial entities (e.g. academic) to become MAHs (C.1.2). This option also brings increased requirements of efficacy and safety for use of hospital exemption (e.g. trial data and good manufacturing practices capability), dedicated pathways for less-complex cell based medicinal products and a regulatory sandbox (C.3.5. and C.3.6.), which may impact the activities of academic researchers and research institutions under this exemption, but should support data collection, safe and efficacious use and ATMP development. Academics and research institutions will also benefit from streamlining 'horizontal' measures such as fee reduction and more scientific support to help non-commercial entities to bring innovative medicines to the market.

8.2 REFIT (simplification and improved efficiency)

The review aims at simplifying the regulatory framework and improving its effectiveness and efficiency thereby reducing the administrative costs borne by companies and administrations[171]. The horizontal measures are envisaged in that regard and most of them will act on the core elements of the authorisation and life-cycle procedures, which are at the centre of this legislation. These measures can be grouped as follows:

Streamlining and acceleration of processes and coordination of the network

The proposed abolishment of the sunset clause and renewal of MAs after five years would avoid unnecessary duplication and a burden on MAHs and regulators[172]. The envisaged reduction in the number of notifiable variations could potentially reduce the administrative costs incurred by MAHs and regulators. For generic applications, in order to avoid duplicative assessments of the same data for medicines containing the same active substance, to reduce administrative costs for both administrations and companies, worksharing procedures and a more efficient repeat use procedure are proposed.

[171] A quantification of these costs is presented in Annex 3.

[172] The latter not adding value regarding safety, given the availability of Periodic Safety Update Reports that accumulate safety data and any impacts on the known benefit-risk balance.

The revision will also look to streamline efficient interaction (early dialogue) between different regulatory authorities (EMA, NCAs, HTA, etc.) as well as synergies between different but related regulatory frameworks, e.g. interplay with BTC framework, medical devices (for certain types of products) and health technology assessments. This, together with a structural simplification of EMA (e.g. as regards the committees) should further reduce the administrative costs for both the administration and the business.

Digitalisation

The envisaged revision aims at an enhanced digitisation of different applications to EMA and NCAs, which should result, overall, in cost reductions. This would induce initial, one-off, costs for the administrations but should bring efficiencies and therefore cost reductions with time. Finally, the envisaged use of the electronic product information, i.e. the electronic leaflet as opposed to paper leaflets, should also, in the long term, adduce additional administrative cost reductions.

Adaptations to accommodate new concepts and support SMEs and non-commercial organisation

The revision foresees adaptations to accommodate new concepts and regulatory processes such as adaptive clinical trials, use of real world evidence, and new uses of health data within the regulatory framework. This should result in cost reductions for businesses and administrations. It also envisages optimising the regulatory support to SMEs and non-commercial organisations. This should in turn result in additional reductions of administrative costs for these parties.

8.3 Simplification and burden reduction for businesses, supporting the one in one out approach

This section evaluates the administrative costs induced by the implementation of the *preferred* option for businesses and citizens/patients, in comparison to the baseline. Moreover, all options include some administrative costs related to horizontal elements, which are also evaluated in comparison to the baseline[173].

As regards companies, there are a number of cost reductions resulting from the implementation of the *preferred* option. The reduction is done for reasons of good policy but also in part to create the financial headroom to introduce new legislative actions and procedures that will inevitably bring additional costs in pursuit of additional social benefits. As a case in point, the strengthening of the environmental risk assessment within the overall assessment process (e.g. in consideration of manufacturing and supply chain issues) will add costs, compared with the current situation, as will the inclusion of environmental issues within post-market authorisation monitoring and the measures on security of supply.

As regards companies, there are also costs reductions resulting from the implementation of horizontal measures which apply to all the options. The revision aims at simplifying the regulatory framework and improving its effectiveness and efficiency thereby reducing the administrative costs. Annex 3 presents the cost for the horizontal measures that relate most directly to streamlining of processes and coordination of network as well as digitisation measures. The table summarises the balance of costs and benefits, and suggests that the measures as proposed may deliver a reduction in compliance costs and administrative burden in the range of €524.5-1,050m for the industry[174].

More specifically:

- The proposed streamlining procedures, including enhanced support, will yield useful cost savings for European pharmaceutical businesses, with estimated cost savings falling in the range of €412.5-825m over the next 15-years.

[173] A quantification of these costs and savings is presented in Annex 3.
[174] Methodological details underpinning the calculations are described in Annex 4.

- The proposed digitalisation measures will provide relatively modest financial savings to industry, given the primary focus is on the integration of regulatory systems and platforms across the EU and support for the re-use of data. Electronic submission will however deliver industry cost savings. These are estimated at €112m-€225m over 15 years.

For citizens/patients, there are many improvements foreseen in all areas of importance[175] but there are no obligations and therefore costs induced by the legislation.

9 HOW WILL ACTUAL IMPACTS BE MONITORED AND EVALUATED?

Indicators for the preferred option, in relation to the core objectives, with suggested data sources and proposed frequency of data collection are presented in table 15. The Commission will review the indicators periodically.

Much of the data collected by EMA are already collected today and published in its annual reports; the new data collected by EMA would result in only a minor additional burden. The burden on the Member States to provide data on the number of shortages, variations and authorised antimicrobials would also be minor, and even further reduced by digitisation. The Commission has access to the IQVIA data and data from the other sources are already being collected.

The development of medicines is a long process and the completion of clinical development plans can take up to 10-15 years. Regulatory protection periods of the preferred option exert their effect up to 11 years after marketing authorisation. For certain measures concerning incentives for innovation, affordability and access, a meaningful evaluation of the revised legislation can take place only 15 years from its application. The Commission will monitor though the indicators and assess the need for an earlier revision.

Table 15 Proposed list of monitoring and evaluation indicators

Specific objective	Monitoring indicators	Data source/frequency
Promote innovation, in particular for UMN	• Number of authorised medicines with new active substance • Number of authorised medicines addressing UMN • Number of authorised antimicrobials • Number of authorised novel antibiotics/transferable vouchers granted • Number of incentives granted for comparative trials • Use of pre-marketing regulatory support (scientific advice, PRIME) • Number of sandboxes used	• EMA data/annual • EMA/annual • EMA and NCAs/annual • EMA/annual • EMA/annual • EMA/annual • EMA/annual
Create a balanced system for pharmaceuticals in the EU that promotes affordability for health systems while rewarding innovation	• Market share of generic and biosimilar medicines • Development of prices of medicines • Member States' pharmaceutical spending	• IQVIA data/biannual • Euripid database, IQVIA data, OECD data/biannual • Eurostat, OECD data/biannual
Ensure access to innovative and established medicines for patients, with special attention to enhancing the security of supply across the EU	• Time from authorisation to market launch • Number of Member States where basket of medicines (both innovative and established medicines) are launched • Number of market access incentives granted • Number of withdrawal of medicines reported </> 1 year in advance • Number of withdrawals for which, as a result of the	• IQVIA data/biannual • IQVIA data/biannual • EMA and NCAs/annual

[175] The legislation aims at improving the flow of cutting-edge treatments for conditions for which there are no effective treatments currently (UMN), reversing the decline in investment in antimicrobial research and encircling the issues driving AMR, incentivising access in all Member States, a broader repurposing, and the generic and biosimilar entry. A more robust ERA will support environmental goals. Measures on security of supply will improve access to medicines.

	notification, measures could be identified to mitigate, prevent or alleviate a critical impact on the health system or on patients of the withdrawal • Total number of shortages • Number of shortages reported </> 6 months in advance, specifying number of critical shortages • Number, root cause and duration of critical shortages and identification of measures that mitigated, prevented or alleviated impact on the shortage • Number of NCAs automatically sharing information with the EMA platform and number of NCAs manually submitting information with the EMA platform	• EMA and NCAs/annual • EMA and NCAs/annual • EMA and NCAs/annual • EMA and NCAs/annual • EMA
Reduce the environmental impact of the pharmaceutical product lifecycle	• Presence of medicines residues in the environment • Consumption of antimicrobials • GHG emissions of EU-based pharmaceutical manufacturers	• Information Platform for Chemical Monitoring that includes data on occurrence of pharmaceuticals in the environment • ECDC annual report on antimicrobial consumption • Eurostat/annually
Reduce the regulatory burden and provide a flexible regulatory framework	• Number of variations • Number of meeting of EMA scientific committees and their working parties • Number of early dialogues/ scientific advice including other public authorities than medicine authorities • Number of scientific advice given to SMEs and academia	• EMA, CMDh and NCAs/annually • EMA/annually • EMA/annually • EMA/annually

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PART 2/2

COMMISSION STAFF WORKING DOCUMENT

IMPACT ASSESSMENT REPORT

Accompanying the documents

Proposal for a Directive of the European Parliament and of the Council on the Union code relating to medicinal products for human use, and repealing Directive 2001/83/EC and Directive 2009/35/EC

Proposal for a Regulation of the European Parliament and of the Council laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, amending Regulation (EC) No 1394/2007 and Regulation (EU) No 536/2014 and repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006

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1 GLOSSARY

Term or acronym	*Meaning or definition*
Accessibility	A medicine becomes accessible to patients once it has been authorised, is being marketed, and can be reimbursed in a Member State.
Affordability	Relates to payments to be made by health systems/public payers and consequently to the sustainability of public funding of the healthcare sector raised through social security contributions or taxes (affordability at macro level).
AMR	Antimicrobial resistance.
ATMPs	Advanced therapy medicinal products (ATMPs) are medicines for human use that are based on genes, tissues or cells, as defined in Article 2 of Regulation (EC) No 1394/2007. See also: Advanced therapy medicinal products: Overview | European Medicines Agency (europa.eu)
Availability	A medicine becomes available once it has been authorised in a Member State or centrally in the EU.
Biological medicine	A medicine whose active substance is made by or derived from a living organism. Biological medicines contain active substances from a biological source, such as living cells or organisms (human, animals and microorganisms such as bacteria or yeast).
Biomarker	Biological molecule found in blood, other body fluids, or tissues that can be used to follow body processes and diseases in humans and animals.
Biosimilar	A biosimilar is a biological medicine that is highly similar to another biological medicine which has already been approved. Biosimilars are approved according to the same standards of pharmaceutical quality, safety and efficacy that apply to all biological medicines.
CAT	The Committee for Advanced Therapies is the European Medicines Agency's committee responsible for assessing quality, safety and efficacy of advanced therapy medicinal products (ATMPs) and following scientific developments in the field.
CAP	The centralised authorisation procedure is The European Union-wide procedure for the authorisation of medicines, where there is a single application, a single evaluation and a single authorisation granted by the European Commission valid throughout the

	European Union.
CBA	Cost-benefit assessment
CHMP	The Committee for Medicinal Products for Human Use is the Agency's committee responsible for human medicines.
Class waiver	Class waivers provide an exemption from the obligation to submit a paediatric investigation plan for a class of medicines, such as medicines for diseases that only affect adults.
Conditional marketing authorisation	Conditional marketing authorisation is the approval to market a medicine that addresses patients' unmet medical needs on the basis of data that is less comprehensive than that normally required. The available data must indicate that the medicine's benefits outweigh its risks and the applicant should be in a position to provide comprehensive clinical data in the future.
COMP	The Committee for Orphan Medicinal Products is the Agency's committee responsible for recommending orphan designation of medicines for rare diseases.
Data protection	Period of protection during which pre-clinical and clinical data and data from clinical trials handed in to the authorities by one company cannot be referenced by another company in their regulatory filings.
EEA	The European Economic Area (EEA) include all EU Member States and also Iceland, Liechtenstein and Norway.
European Joint Programme on Rare Diseases	The is co-fund between EU Member States' research funding agencies and the Commission under the EU research & innovation funding programme Horizon 2020. It aims to create an effective rare diseases research ecosystem.
EMA	The European Medicines Agency ('the Agency') is an EU agency founded in 1995 which is responsible for the scientific evaluation, supervision and safety monitoring of medicines, both human and veterinary, across Europe. (https://www.ema.europa.eu/en).
ERN	European reference networks (ERNs) are virtual networks involving healthcare providers across Europe. Directive 2011/24/EU on patients' rights in cross-border healthcare together with Delegated Decision 2014/286/EU and Implementing Decision 2014/287/EU provide for the setting up of ERNs, 24 of which were established in 2017. The purpose of these networks is to facilitate discussion of complex or rare diseases and conditions that require highly specialised treatment,

	and concentrated knowledge and resources.
Evergreening	"Evergreening" strategies extend the effective protection period and thus allow drug companies to maintain a market share after their protections expire by introducing "follow-on drugs" - those with slight changes made to them after expired protections that would normally allow generic competitors to enter the market.
Extension of marketing authorisation	A change to a marketing authorisation which fundamentally alters its terms. Such changes may concern the active substance, the strength, the pharmaceutical form and/or the route of administration.
FDA	United States Food and Drug Administration.
Generic medicine	A generic medicine contains the same active substance(s) as the reference medicine, and it is used at the same dose(s) to treat the same disease(s). The generic can only be marketed after expiry of the data and market protection.
Global marketing authorisation	A global marketing authorisation contains the initial orphan marketing authorisation and all additional indications granted to the marketing authorisation holder of the initial authorisation.
HUMN	High Unmet Medical Need
HTA	A health technology assessment (HTA) is the systematic evaluation of the added value of a new health technology compared to existing ones. It is a multidisciplinary process to evaluate the social, economic, organisational and ethical issues associated with a health intervention or health technology. The main purpose of conducting an assessment is to inform pricing & reimbursement decision-making.
Horizon 2020 (H2020)	EU Framework Programme for Research & Innovation for the period 2014-2020.
Horizon Europe (HE)	EU Framework Programme for Research & Innovation for the period 2021-2027.
IA	An impact assessment must identify and describe the problem to be tackled, establish objectives, formulate policy options, assess the impacts of these options and describe how the expected results will be monitored. The Commission's impact assessment system follows an integrated approach that assesses the environmental, social and economic impacts of a range of policy options, thereby ensuring that sustainability is an integral component of Union policymaking.

IQVIA	IQVIA is a contract research and analytical services organisation that collects data including global pharmaceutical sales data (https://www.iqvia.com/). These sales data were used for this IA.
Magistral/officinal formula	A medicinal product prepared in a pharmacy in accordance with a medical prescription or according to the prescriptions of pharmacopoeia and intended to be supplied directly to patients served by the pharmacy.
Medical condition	Any deviation(s) from the normal structure or function of the body, as manifested by a characteristic set of signs and symptoms (typically a recognised distinct disease or a syndrome).
Marketing authorisation	The approval to market a medicine in one, several or all European Union Member States.
Marketing authorisation application	An application made to a European regulatory authority for approval to market a medicine within the European Union.
Market exclusivity	The period after the marketing authorisation of an orphan medicine when similar medicines for the same indication cannot be placed on the market. Under the current legislation, the market exclusivity has a duration of 10 years.
Market protection period	Part of the regulatory protection period, supplementing the data protection period. It is the period of protection during which generics cannot be placed on the market.
Megatrends	Megatrends are long-term driving forces that are observable now and will most likely have significant influence on the future. Megatrends are closely interlinked between each other and simultaneously affect many different stakeholders. Thus, a systemic and global understanding of the issue under study is necessary to fully picture and illustrate the dynamics at stake. See also: The Megatrends Hub | Knowledge for policy (europa.eu)
Neonatology	A subspecialty of paediatrics consisting of medical care for new-born infants, especially the ill and premature.
Non-cash benefits	Non-cash or intangible benefits are benefits expected from improved actual treatment, resulting in reduced mortality, improved quality of life and time saved by informal carers.
“Off-label” use	Use of a medicine for an unapproved indication or in an unapproved age group, dosage, or route of administration. E.g. use of a medicine in children that is authorised for adults

Oncology	A branch of medicine that specialises in the prevention, diagnosis and treatment of cancer.
“On-label” use	A medicine is being used as described in the marketing authorisation.
Orphan condition	A medical condition, that meets the criteria of a life-threatening or chronically debilitating condition affecting no more than five in 10 thousand persons in the EU defined in Article 3 of Regulation (EC) No 141/2000.
Orphan designation	A status assigned to a medicine under development intended for use against a rare condition. The medicine must fulfil certain criteria for designation so that it can benefit from incentives such as market exclusivity.
Orphan indication	The proposed therapeutic indication at the time of the orphan designation. This specifies if the medicinal product subject to the designation application is intended for diagnosis, prevention or treatment of the orphan condition.
Orphan-likes	Orphan-like medicinal products to treat rare diseases which entered the EU market from the United States before 2000, when there was no special legislation in place.
Orphan Regulation	Regulation (EC) No 141/2000 on medicinal products for rare diseases
Payer	An entity responsible for financing or reimbursing healthcare e.g. national or private health insurance systems
Paediatric Regulation	Regulation (EC) No 1901/2006 on medicinal products for medicines for children
PDCO	The Paediatric Committee is the Agency's scientific committee responsible for activities associated with medicines for children. It supports the development of such medicines in the European Union by providing scientific expertise and defining paediatric need.
PIP	A paediatric investigation plan is a development plan designed to ensure that the data required to support the authorisation of a paediatric medicine are obtained through studies of its effect on children.
PUMA	The paediatric-use marketing authorisation is a dedicated marketing authorisation covering the indication(s) and appropriate formulation(s) for medicines developed exclusively

	for use on the paediatric population.
QALYs	Quality-adjusted life years refers to a measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to one year of life in perfect health. QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality-of-life score (on a 0 to 1 scale). It is often measured in terms of the person's ability to carry out the activities of daily life and freedom from pain and mental disturbance.
Rare disease	Rare diseases are diseases with a particularly low prevalence; the European Union considers diseases to be rare when they affect no more than 5 per 10,000 people in the European Union.
Regulatory data protection	Regulatory data protection refers to a period in which a generic applicant cannot refer to the marketing authorisation holder's data to obtain a marketing authorisation. For human medicines the regulatory data protection period is 8+2 years.
Repurposed medicines	Existing medicines investigated for new therapeutic indications.
R&D	Research & Development
RPV	Regulatory Protection Voucher
RSB	The Regulatory Scrutiny Board is an independent body of the Commission that offers advice to the College of Commissioners. It provides a central quality control and support function for the Commission's impact assessment and evaluation work. The Board examines and issues opinions and recommendations on all the Commission's draft impact assessments and its major evaluations and fitness checks of existing legislation.
ROI	Return on investment
SDGs	17 Sustainable Development Goals were adopted by the United Nations in 2015 as a universal call to action to end poverty, protect the planet, and ensure that by 2030 all people enjoy peace and prosperity.
SMEs	Micro, small and medium-sized enterprises
SPC	The supplementary protection certificate is an intellectual property right that serves as an extension to a patent right. The patent right extension applies to specific pharmaceutical and plant protection products that have been authorised by regulatory

	authorities.
Sponsor	Legal entity responsible for submitting an application for orphan designation to the EU.
SWD	Staff working documents are required to present the results of all impact assessments and evaluations/fitness checks.
TEV	Transferable exclusivity voucher.
Therapeutic indication	The proposed indication for the marketing authorisation. A medical condition that a medicine is used for. This can include the treatment, prevention and diagnosis of a disease. The therapeutic indication granted at the time of marketing authorisation will be the result of the assessment of quality, safety and efficacy data submitted with the marketing application.
UMN	Unmet Medical Need
Well-established use	When an active ingredient of a medicine used for more than 10 years and its efficacy and safety have been well established. In such cases, application for marketing authorisation may be based on results from the scientific literature only.

1 INTRODUCTION: POLITICAL AND LEGAL CONTEXT

In the European Union (EU) up to 36 million citizens are affected by one of the over 6,000 rare diseases[1] currently recognised. Rare diseases are those that affect less than 5 out of every 10,000 people. These diseases are often chronic and life-threatening; around 80% of rare diseases are of genetic origin and, of those, 70% already start in childhood[2]. For these patients treatment was either limited or non-existent in the 1990s. Children as a whole population group faced a similar challenge. Developing medicines for rare diseases and for children is a high-risk and expensive endeavour. In addition to limitations in scientific knowledge, developing those medicines was seen by the pharmaceutical industry as economically unattractive due to generally small market size[3]. Moreover, research and development, including conducting clinical trials, often multi-site and with small populations, is considered to be complex[4].

The 'Orphan Regulation'[5] and the 'Paediatric Regulation'[6] were adopted, in 2000 and 2006, to respond to these specific challenges. They provide developers with targeted incentives, rewards and obligations, as an add-on to the *general* EU pharmaceutical legislation[7] [8].

Over the intervening decades, a positive change resulting from these policy interventions has been observed in the Joint Evaluation conducted in 2020. While the share of orphan medicines in the total sale of branded medicines has increased worldwide from 6% in 2000 to over 16% in 2016, and it is expected to reach 21% in 2022[9] the average time to market from the date of marketing authorisation to patient *access* in the various Member States still differs enormously[10]. Furthermore, there have been wide-ranging developments and discoveries in science, which, alongside the globalisation of the pharmaceutical sector, the public health systems' sharper focus on unmet medical needs of patients and the disparities and the budgetary impacts of medicines call for revisiting the policy intervention in the area of rare diseases and medicines for children.

The revision of the EU legislation on medicines for rare diseases and medicines for children is part of the implementation of the Pharmaceutical Strategy for Europe[11], which includes the revision of the general pharmaceutical legislation. The revisions are intended to work synergistically and the interaction between them is taken into account in this impact assessment (IA), which analyses policy options for addressing the shortcomings and challenges highlighted by the Joint Evaluation and the lessons learnt from the COVID-19 pandemic.

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[1] See also Rare diseases (europa.eu).

[2] See also Section 1 of the Staff Working Document on the Joint Evaluation of Regulation (EC) No 1901/2006 on medicinal products for paediatric use and Regulation (EC) No 141/2000 on orphan medicinal products https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:52020SC0163, referred to as the "Joint Evaluation".

[3] Children are not a uniform population due to their physiological characteristics. Specific clinical trials have to be designed and conducted in preterm children, infants, toddlers, children and adolescent,

[4] Idem.

[5] Regulation (EC) No 141/2000 on medicinal products for rare diseases, https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32000R0141.

[6] Regulation (EC) No 1901/2006 on medicines for children, https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32006R1901.

[7] Legal framework governing medicinal products for human use in the EU (europa.eu).

[8] Regulation (EC) 726/2004 and Directive 2001/83/EC.

[9] OECD, New Health Technologies: Managing Access, Value, and Sustainability, 2017.

[10] Patients in Germany, the Scandinavian countries and France have access to medicines for rare diseases in a much shorter time than patients in Greece, Ireland, Bulgaria, Romania and Croatia. See also: https://doi.org/10.1016/j.jval.2018.01.007

[11] Pharmaceutical Strategy for Europe.

1.1 Legal context

1.1.1 General pharmaceutical legislation

The Orphan and Paediatric Regulations cannot be seen in isolation. They complement the provisions of the general EU pharmaceutical legislation. The general legislation harmonises the way medicines are authorised across the EU and foresees that a medicine may only be placed on the market following a positive benefit-risk assessment of its quality, safety and efficacy by a competent authority. Medicines may either be authorised centrally (CAP procedure)[12] by the European Commission on the basis of a positive scientific assessment by the European Medicines Agency ('the Agency') or nationally by an individual or a group of Member States. For orphan medicines, the use of the CAP is mandatory[13]. Such authorisation gives the right, but not the obligation, to place the medicine on the market in all Member States. Consequently, a CAP medicine is not necessarily *accessible* in all Member States. Its actual placing on the market depends on the launch strategy of companies and for most prescription medicines on national pricing and reimbursement decisions.

The general pharmaceutical legislation provides for regulatory data protection of 10 years[14] as a standard incentive for all newly authorised products, also called originators (including medicines for children and rare diseases). During that period companies cannot launch cheaper copies of medicines (generic and biosimilar)[15]. Given that the Orphan and Paediatric Regulations provide specific (additional) incentives and rewards, the system of incentives represents an important interplay between the general and the specialised legislation. To note that generic entry is also influenced by the duration of IP protection, including supplementary protection certificates ('SPC')[16]. The general legislation moreover regulates other issues like the scientific requirements for authorisation, the safety monitoring (pharmacovigilance), as well as manufacturing, distribution and advertising. Those provisions apply to all medicines, including those for rare diseases and children.

A detailed description of the EU legislative framework on medicines and the interplay between the general and specialised legislation is available in Annex 6, 7 and 12.

1.1.2 Regulation on medicines for rare diseases

The Orphan Regulation aims at enabling research, development and authorisation of new medicines for rare diseases through specific incentives ('market exclusivity').

An orphan medicine is a medicine for a life-threatening or chronically debilitating disease affecting no more than 5 in 10,000 people in the EU (prevalence criterion) or a medicine that, without incentives, would be unlikely to generate sufficient return to justify the investment (return of investment criterion). No satisfactory treatment for such diseases should exist in the EU, or, if it exists, the product should provide significant benefit to patients affected by that condition in comparison with the existing treatment.

The Orphan Regulation establishes a two-step procedure:

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[12] The CAP is laid down in Regulation 726/ 2004. Authorisation procedures - The centralised procedure (europa.eu).

[13] Medicines for children can be authorised under the CAP, but no obligation is in place. The marketing authorisation holder can decide which procedure to follow.

[14] Meaning the period of protection during which pre-clinical and clinical data and data from clinical trials handed in to the authorities by one company cannot be referenced by another company in their regulatory filings.

[15] Unless they obtain the data supporting the authorisation with their own clinical trials.

[16] They apply to specific pharmaceutical and plant protection products that have been authorised by regulatory authorities. SPCs aim to offset the loss of patent protection for pharmaceutical and plant protection products that occurs due to the compulsory testing and clinical trials these products require prior to obtaining regulatory marketing approval. See also: Supplementary protection certificates for pharmaceutical and plant protection products (europa.eu).

- **Designation prior to marketing authorisation**: a company may request at any stage of development an 'orphan designation' (recognising the potential ability of the future medicine to address a rare disease), based on an opinion by the Agency and a Commission decision. Such designation may allow developers (researchers, SMEs[17], not-for profit entities, big companies) to secure financial support for research and development (R&D), for example through the EU research framework[18] or national funding mechanisms. A designation may also help SMEs attracting risk capital provided by investors. In addition, it may enable a product to receive dedicated support from the Agency, such as scientific advice for the design of trials[19].
- **Authorisation**: if, at the time of granting the marketing authorisation, the evidence confirms continued compliance with the designation criteria, an orphan medicine will benefit from 'market exclusivity', providing a monopoly-like protection for 10 years from competition from *similar* medicines for the same therapeutic indication. The protection goes beyond regulatory protection provided by the general pharmaceutical legislation as it protects against the competition from all *similar* products, and not only against generics. The market exclusivity period may be shortened to 6 years if it is established that the criteria are no longer met, and that the product is sufficiently profitable.

1.1.3 Regulation on medicines for children

The Paediatric Regulation works with a mix of obligations and rewards. It compels companies to screen any new medicine (especially, adult medicines) for possible use in children. To compensate for the additional costs incurred[20], it provides rewards (prolongation of the duration of the supplementary protection certificate) once the obligation is fulfilled.

The Regulation requires companies at an early stage in the development of any new medicine to engage with the Agency, by either agreeing on a paediatric clinical research and development programme (paediatric investigation plan – 'PIP), or obtaining a derogation ('waiver') from this obligation. Such waivers may be granted if the product is dangerous for children, if the disease concerned does not exist in children or if the product is not expected to not bring significant benefits to children compared to existing treatments. The agreed clinical studies must be conducted in parallel with the adult studies, unless the Agency agrees that some or all of the studies with children should be conducted later. Such 'deferrals' are granted if the paediatric studies would delay the marketing authorisation for adults or if information deriving from adult studies are needed before initiating paediatric research. Once a PIP is completed and the results are included in the marketing authorisation and even if the studies show that the product is unsuitable for children, the company is eligible for one of two mutually exclusive rewards:

- An entitlement to a six-month extension of the SPC; or
- A two-year extension of the market exclusivity if the product is an orphan medicine.

Both extensions cover the *entire* product, including the "adult" part. However, the SPC extension is not automatic. An application must be filed to the national patent office and that two years before the SPC expires[21].

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[17] Small and medium-sized enterprises (SMEs) are defined in the EU recommendation 2003/361.
[18] Research and Innovation, Horizon Europe.
[19] Scientific advice and protocol assistance | European Medicines Agency (europa.eu).
[20] Cost of conducting clinical studies in children and administrative costs to comply with the obligation.
[21] Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009.

To drive the development of indications for children for *existing* products, which are no longer covered by a patent (repurposing), a paediatric-use marketing authorisation ('PUMA') entitles to 10 years protection from generic competition covering the newly authorised paediatric indication[22].

1.2 Political and policy context

This initiative is part of the **Pharmaceutical Strategy for Europe** (the 'Strategy') aiming to create a future proof regulatory framework, to foster patient access to innovative and affordable medicines, to support the competitiveness and innovative capacity of the EU's pharmaceutical industry and ensure robust supply chains so that Europe can provide for the needs of its patients. It supports the EU's ambition to build a stronger **European Health Union**[23], in which all EU countries prepare and respond together to health crises, medical supplies are available, affordable and innovative, and countries work together to improve prevention, treatment and aftercare for diseases such as cancer.

Together with the revision of the general pharmaceutical legislation the review of the Orphan and Paediatric Regulation therefore aim to address similar problems and achieve common objectives: promoting innovation to better address unmet medical needs, creating an enabling environment to improve affordability and access of patients to innovative medicines and reducing regulatory burden, recognising some trade-offs between those objectives. This impact assessment takes into account this overlap in the description of the problem drivers and through aligning the methodology and the design of the options. Planned modulations to the incentives to address access and affordability in the general pharma legislation have therefore been considered when designing changes to the orphan market exclusivity and vice versa. Moreover, paediatric and orphan medicines will benefit from new instruments to support innovative products, provisions to improve access and affordability, as well as measures for simplification like an increased digitalisation of the system (such as the electronic submission of applications) introduced by the revision of the general pharmaceutical legislation.

1.2.1 Link with other initiatives

As highlighted, the Orphan and Paediatric legislation regulate only specific aspects in the life-cycle of these medicines. They can be considered as an enabling element in a broader landscape of policy interventions. Another important element in this landscape is the direct funding of **research and development**, supported through the EU Horizon 2020 and Horizon Europe[24] programmes. From 2007 to 2020, the EU supported research on rare diseases substantially, with more than €2.9 billion attributed to over 1000 R&I projects (approximately €205 million/year from 2007-2013 and €215 million/year from 2014-2020[25]). Under these programmes, funding is mostly allocated to pre-competitive research for catalysing innovation in drug development in the medium and long term. In this way, it is expected that these public investments provide the science needed from which new orphan medicines may be discovered later. In addition, the European Joint Programme on Rare Diseases[26], co-funded between Member States and the Commission, also aims to contribute to more and better research on rare diseases. The European Commission also foresees under its Horizon Europe and health research priority, a European Partnership co-fund on Rare Diseases[27], which should be operational by mid-2024 and it will bring together a broad range of research and

[22] A generic medicine is a medicine that is developed to be the same as a medicine that has already been authorised. Its authorisation is based on efficacy and safety data from studies on the authorised medicine. A company can only market a generic medicine once the protection periods for the original medicine has expired.
[23] The European Health Union was announced by Ursula von der Leyen, President of the European Commission, in 2020, European Health Union | European Commission (europa.eu).
[24] EU rare diseases research
[25] Data received from DG RTD.
[26] The European Joint Program on Rare Diseases.
[27] Draft Proposal for a European Partnership under Horizon Europe – Rare Diseases, 18/02/2022.

innovation actors. Moreover, the EU RD Platform[28] which tackles the fragmentation of rare disease patients data contained in scatted registries across Europe, provides a Pan-European infrastructure to securely access and share patient data for advancing clinical research and healthcare delivery.

The EU's Mission on Cancer[29] together with the initiatives under **Europe's Beating Cancer Plan**[30] aim at boosting research and development of novel treatments for cancer but also to improve its screening and early detection. These will complement the paediatric regulation ensuring that cancer, which is the first cause of death by disease post infancy, will be tackled in a multi-facet way, from prevention and diagnosis, to treatment to quality of life of patients.

The new **Clinical Trials regulation**[31] allows as of 2022 a more efficient process for the approval of multinational trials through a single application and a common assessment. This facilitates the conduct of trials in small populations like orphan medicines and children, which are often multi-country trials. The Regulation will also increase transparency on which trials are ongoing in the EU and on their results.

Not only basic research but also the early and correct diagnosis of a rare disease is a challenge, which cannot be directly addressed by the Orphan and Paediatric Regulation. The **European Reference Networks** (ERNs)[32] support the diagnosis and treatment of patients suffering from rare diseases and help to connect experts and health professionals in a virtual network.

The **European Health Data Space**[33] will provide a common framework across Member States for the access to high-quality real world health data. The data that will become accessible are expected to allow progress in research and development of medicines. The health data space is expected to benefit in particular small patients' populations, such as the people living with a rare disease. This is due to the fact that at the moment health data of such population groups are scattered across Member States.

The **Intellectual Property Action Plan**[34] under the Industrial Strategy[35] includes the modernisation of the system of supplementary protection certificates (SPC) in the form of a "Unitary SPC"[36] which does not intend to modify the maximum period of a SPC, but may lead to wider coverage of SPCs (the major reward for developers for medicines for children).

1.2.2 The pharmaceutical ecosystem

The orphan and paediatric legislation intervene in a complex ecosystem. On the *supply side*, the pharmaceutical sector is characterised by two main types of companies: originator companies and generic companies[37]. Originator companies can range from 'Big Pharma' to biotech and SMEs concentrating on certain niche products. In the orphan sector, 42 % of the authorised products have been *developed* by SMEs[38] although the number of marketing authorisation holders among SMEs tend to be lower as they may have been acquired by larger pharmaceutical companies during the

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[28] https://eu-rd-platform.jrc.ec.europa.eu/_en
[29] Implementation Plan, European Missions – Cancer.
[30] Communication - Europe's Beating Cancer Plan.
[31] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC.
[32] Overview European Reference Networks (europa.eu); ERNs are regulated by Directive 2011/24/EU.
[33] COM(2022) 197 final.
[34] COM(2020)760 final.
[35] COM(2021) 350 final.
[36] Medicinal & plant protection products – singles procedure for the granting of SPCs
[37] Generic companies 'copy' a product that has already been authorised, once protection periods have expired (at a lower price, therefore addressing affordability issues in health systems).
[38] Data from EMA.

development phase of the orphan product.[39]. Generally, pharmaceutical companies in the EU are a large funder of pharmaceutical R&D, making the biggest contribution to research investment in 2019, with over €37 billion. The sector provides 800 000 direct jobs and a €109.4 billion trade surplus[40]. The *demand* side of the pharmaceutical sector is rather unique as it is characterised by a complex ecosystem of agents including patients, doctors, hospitals, health technology assessment bodies, and payers. For prescription medicines, the final consumer (i.e. the patient) differs from the decision maker (generally the prescribing doctor) and very often also from the payer (generally in the EU the national health system, and ultimately the taxpayers)[41].

A description of the pharmaceutical ecosystem is provided in Annex 7.

1.2.3 International context

Medicines development is global. R&D investment and regulatory frameworks are therefore influenced by developments in other regions. The structural features of the US regulatory system for orphan and paediatric medicines are very similar to the EU system and they have influenced each other over the years. However, differences exist with regard to other support schemes and the demand/access side, which make the US market very attractive for developers.

For *orphans*: the US legislation provides seven years of market exclusivity, which is lower than in the EU. But the US has higher annual figures for both designations and marketing authorisations for orphan medicines. This is mostly explained by tax incentives (50% of development cost is tax deductible in the US) and by differences in eligibility criteria for obtaining an orphan designation. In the EU, rare diseases are defined as affecting smaller numbers of people than in the US. Some medicines not eligible for orphan designation in the EU are thus considered orphan in the US. Moreover, in the EU the eligibility criteria are checked again during the marketing authorisation stage, leading to some products losing their orphan status as they can no longer demonstrate their significant benefit. This is not the case in the US.

For *paediatrics*: similar to the system in the EU the US also requires companies to conduct paediatric study programmes. Their completion is rewarded with an additional protection period (6 months extension of the existing patent or exclusivity – same as in the EU). The number of medicines for children authorised is very similar between the EU and the US and it is 6 times higher than in Japan where no paediatric legal framework exists and double compared to Canada where a legislative framework exists but it is not compulsory.

There is strong global collaboration between EMA and US Food and Drug Administration (FDA) both in the areas of orphans and paediatrics, and together with other non-EU regulators.

Interestingly, also in the US a discussion gains pace pointing to changes in the orphan medicine market, where some high expenditure orphan medicines have generated significant revenues putting into question the (continued) existence of the general market failure that was at the origin of the policy intervention[42].

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[39] A good example of an initially small SME, developing medicinal products, is Shire. It came to life as a start-up in 1986 and was involved in the development of a wide range of medicinal products. Shire began broadening its scope into rare diseases with the acquisition of TKT (an orphan drug company) in 2005. It continued acquiring other pharmaceutical companies and forging partnerships until Takeda took over Shire in 2018 in a $62 billion acquisition. Before this acquisition of Shire, roughly a third of Takeda's experimental drugs carried an Orphan Drug Designation, while adding Shire took that figure up to roughly 50% of Takeda's pipeline of orphan designations. See also: A history of Shire (pharmaphorum.com) and Shire deal done, Takeda turns to task of forging top pharma | BioPharma Dive

[40] Section 1 of the Pharmaceutical Strategy for Europe.

[41] European pharmaceutical research and development, European Parliament Research Service, p. 7.

[42] High-expenditure Medicare drugs often qualified for Orphan Drug Act incentives designed to encourage the development of treatments for rare diseases, US Department of Health and Human Services.

Further information on the international context can be found in Annex 8.

1.2.4 United Nations' Sustainable Development Goals (UN SDGs)[43]

This initiative is in line and supports the achievement of the UN SDGs, in particular SDG 3 ('ensure good health and well-being at all ages') by addressing the insufficient development of medicines in areas of unmet medical needs. The objectives and proposed measures aimed at tackling unmet medical need, affordability and unequal access to medicines across the EU are linked to SDG 3. More details are provided in Annex 3.

1.2.5 COVID-19

The COVID-19 crisis has impacted EU health systems. Most of the respondents to the public consultation[44] considered that global attention and resources rapidly shifted towards COVID-19 and R&D efforts in the areas of medicines for rare diseases and children were reduced. On the other hand, more innovative ways to involve children in clinical trials and increased flexibility and efficiency in conducting them may have positive impacts. COVID-19 also showed the possibility for an acceleration and streamlining of some regulatory procedures (e.g. PIP agreements and compliance checks for COVID-19 vaccines). These learnings inform some of the proposed changes to streamline procedures and other simplifications which are examined in this intervention.

2 PROBLEM DEFINITION

2.1 What are the problems?

The Joint Evaluation showed that both Regulations have contributed to fostering the development and authorisation of medicines for rare diseases and children in the past 20 years. They have redirected private and public investments towards these previously neglected areas and favored the creation of an EU research environment for both areas. However, the interventions were not the only factor contributing to these results. They represented an important enabler complementing other policies like increased research funding[45].

The number of medicines for patients with rare diseases has increased[46] and have reached a higher number of patients. Similarly, the number of clinical trials involving children and, consequently, the development of new medicines for them increased. Companies consider now new paediatric developments as an integral part of pharmaceutical development

Despite these positive developments, four main problems have been identified[47]:

1. Medical needs of patients with rare diseases and children are not sufficiently met;
2. Affordability of medicinal products is a challenge for healthcare systems;
3. Unequal access to medicines across the EU;
4. The system caters insufficiently for innovation and creates unnecessary burden.

These problems ultimately impact patients but also concern a broader range of stakeholders including national public authorities, civil society and the pharmaceutical industry.

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[43] THE 17 GOALS | Sustainable Development (un.org).
[44] Medicines for children & rare diseases – updated rules (europa.eu).
[45] See also Sections 1.2 and 1.3 of this SWD.
[46] The Joint Evaluation (Section 6) found that during the time period 2000-2017, 142 orphan medicines have been authorised. These medicines have helped up to 6.3 million European patients.
[47] The problems were identified in the main findings of the Joint Evaluation (Section 6) and are common to orphans and all other medicines covered by the general pharmaceutical legislation.

The findings from the evaluation were confirmed by the feedback received on the inception impact assessment[48], the public and targeted surveys and the desk analysis conducted in the course of this IA. The summary below provides updated information on the problem definition further to what was presented in the Joint Evaluation.

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

The Orphan Regulation fostered R&D in the field of medicines for rare diseases in the EU. To date, the Commission has authorised more than 200 medicines for rare diseases and designated around 2000 molecules in development. However, 95% of the over 6000 recognised rare diseases still have no treatment option[49] and for those that have, the majority of the treatments are symptomatic and not curative. Both areas can consequently be considered as areas of *high* unmet medical need (HUMN) for patients suffering from rare diseases. The current system has no instruments to channel developments in certain areas of particular need for patients. Investors therefore tend to prioritise the most commercially lucrative orphan disease areas[50], as well as areas where risks of failure due to insufficient scientific knowledge is less, rather than those with higher public health benefits.

Concerning medicines for children, developments are still driven by *adult* developments. When the therapeutic need for adults diverge from the ones of children, like in the case of paediatric cancers, mental and behavioral disorders or treatments for neonates, the number of treatments available is limited[51]. Furthermore, currently, a PIP is not required where an adult product is intended for a disease that does not exist in children. However, such a product could, on the basis of scientific evidence, also be effective against a different disease. This may for example be a product developed to treat an adult cancer (non-existing in children) that could also be effective to treat a different type of cancer in children.

All stakeholders agreed that developments in areas of UMN for patients should be better supported, even if some representatives from public authorities raised concern that such products should not come with excessive costs for their health systems.

2.1.2 Affordability of medicines is a challenge for health systems

Pricing and reimbursement decisions and pharmaceutical expenditure are national competences and outside the scope of the orphan and general pharmaceutical legislation. Decisions vary across the EU. However, under national legislation, orphan medicines often benefit from separate budgets, lower requirements for data for pricing and reimbursement decisions and substantial willingness to pay, sometimes at a very high cost, often under pressure by advocacy groups and public opinion[52]. To compensate for uncertainties with regard to cost-effectiveness existing at the time of Health Technology Assessment, some Member States have put in place managed entry agreements (MEAs)[53]. The separate budgets for orphans may allow companies to charge higher individual prices for their orphan products, although MEAs can reduce the prices, making coverage and payments to companies or rebates paid by companies conditional on product performance[54].

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[48] Inception impact assessment.
[49] Section 3 of the Joint Evaluation.
[50] Including in areas where an active ingredient of a medicine has been used for more than 10 years and its efficacy and safety have been well established. In such cases, the application for marketing authorisation may be based on results from the scientific literature only (but currently still gets a market exclusivity of 10 years) – well established use.
[51] 10 years EMA technical report to the Commission, table 11.
[52] Section 5.1 of the Joint Evaluation.
[53] Agreements between pharmaceutical companies and healthcare payers that allow for coverage of new medicines while managing uncertainty around their financial impact or performance. See also: HTA Overview (europa.eu).
[54] OECD Health Working Papers No. 115.

The average list price of new medicines is fast increasing, especially for orphan medicines[55]. The consequences of high prices are affordability problems for patients and sustainability of health systems. Pharmaceutical expenditure in Europe is largely subsidised by national health systems in order to ensure the adequate provision of medicines to all their respective citizens. Orphan medicines did not always have a measurable impact on public health budgets; high individual treatment prices coupled with very small patient populations had an almost invisible effect at systemic level. However, the last decade brought an increasing number of new orphan medicines with very complex technology (CAR-T cell therapies, gene-edited therapies) and 6-7 digit price tags[56]. This is not only a problem in the EU, as the US is facing the same issue[57].

Prices for medicine vary significantly between Member States. For a sample of medicines, it was also shown that list prices were the highest in Germany and the lowest in many different EU countries but never in the ones with lower GDP per capita like Bulgaria or Romania[58].

Overall, the annual total expenditures on healthcare in the EU is around 10% of GDP[59] and this pharmaceutical spending specifically puts pressure on health systems. Medicines in the hospital account for over 20-30% of hospital expenditures and are growing[60].

The public debate is increasingly focused on medicine prices. Although the discussion is not restricted to orphan medicines, such products have received particular scrutiny, given the market exclusivity offered. In addition, it has been observed that some producers substantially increased the price of newly-authorised orphan medicines that were previously available to patients as a magistral or officinal formula (well-established use[61]) at a much lower price[62]. These price increases seem to bear no relation to actual R&D costs which is normally lower for well-established use medicines. The latter accounted, together with so called repurposed products[63], for 19% of orphan medicines in the EU[64].

Furthermore, an orphan medicinal product can currently be authorised for several orphan indications, leading to *separate* and consecutive 10-years of market exclusivity protection for each new indication authorised[65]. This delays the on-label use of generic and biosimilar products for those authorisations.

Generic and biosimilar entry and competition is an important factor to achieve lower prices, broadening patients' access and alleviating healthcare costs. Generic entry does however not always happen, due to the usually small market size for orphan products (fewer patients), which can make the market commercially less attractive for generic manufacturers. Looking at the 36 products (out of 190 orphan products in the period 2000-2020) for which the market exclusivity already expired, 11 saw at least one generic competitor with sales.

Concerning medicines for children, their price depends on the price of the "adult" product. No specific issues on high prices of medicines only for children were identified. However, the rewards

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[55] OECD, New Health Technologies: Managing Access, Value, and Sustainability, 2017
[56] OECD, New Health Technologies: Managing Access, Value, and Sustainability, 2017
[57] Orphan drugs in the United States, IQVIA.
[58] Zaprutko T. et al. Affordability of medicines in the European Union. *PLoS One*. 2017;12(2):e0172753.
[59] Eurostat System of Health Accounts, 2019 data. Recent joint projections from the European Commission and Member States (2021) indicate that public spending on healthcare, as a share of GDP, is projected to increase by a factor of 1.1 between 2019 and 2040.
[60] European Commission, State of health in the EU: companion report 2019 (ISBN 978-92-76-10194-9).
[61] I.e. when an active ingredient of a medicine has been used for more than 10 years and its efficacy and safety have been well established. See also: Well-established use | European Medicines Agency (europa.eu)
[62] ACM imposes fine on drug manufacturer Leadiant for CDCA's excessive price | ACM.nl
[63] Existing medicines that are investigated for new therapeutic indications.
[64] See also Section 5.2 of the Joint Evaluation; Data until 2018.
[65] So called indication stacking. See also Section 5.2.3. of the Joint Evaluation.

granted in accordance with the paediatric Regulation (SPC prolongation) may have the effect of delaying generic entry for the adult products and consequently on their affordability.

The rising costs of medicines were identified as key concerns for academics, healthcare professionals, public authorities and civil society stakeholders.

2.1.3 Unequal access to medicines across the EU

All consulted stakeholder groups[66] agree that patients' access to authorised medicines is a major issue. Out of the 190 **orphan** medicinal products developed and authorised in the 2000-2020 period, data were collected for 155 of them[67]. It was found that only about half of them are currently accessible to patients in a majority of Member States. Moreover, patient access to orphan medicines varies considerably between Member States. Germany, France or Italy for instance have a high market uptake, with more than 100 medicines for rare diseases available. On the contrary, countries like Lithuania, Bulgaria or Ireland had less than 50 orphan medicines available.[68] Compared with standard medicines, access is worse for orphan medicines[69].

The launch of an indication or medicine **for children** is often linked to the launch of the corresponding adult product. It has been observed that companies tend to rely on a staggered roll-out of any new product for adults across the EU, resulting in delays until the product for children is accessible[70].

According to all stakeholders consulted, enabling access to affordable medicines is among the areas where the EU pharmaceutical legislation has been less effective.

A description on the EU system for pricing and reimbursement is provided in Annex 10

2.1.4 The system caters insufficiently for innovation and creates unnecessary burden

Advances in science, such as advanced therapy medicinal products, personalised medicine approaches[71] and the use of biomarkers[72] have already allowed to better target treatments for patients suffering from a rare disease[73]. At the same time, these new products have challenged the current system of orphan designation, which relies on criteria which must be met if a product is to receive an orphan designation[74].

The Paediatric Regulation obliges to define at a very early stage the full clinical development plan for paediatric medicines. However, for innovative paediatric products, a detailed development plan is often decided step by step while clinical data are collected, therefore the legislation create the need to frequent modifications of the agreed PIPs causing increased administrative burdens for applicants and delays in the completion of the PIP and consequently of the authorisation of the use of the medicine in children. Moreover, the provisions on medicines for children allow to exclude from the obligation to conduct clinical studies in children certain medicines developed for diseases

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[66] Synopsis report (Annex 2 to this SWD) and Impact assessment on the general pharmaceutical legislation.
[67] Based on analysis of the IQVIA data covering the availability of medicines for rare diseases across 24 Member States
[68] See also Section 5.1.2 of the Joint Evaluation.
[69] Our findings in Section 6.2 show that orphan medicines become accessible within 10 years of authorisation for a *smaller* proportion of the EU population and that the pace is slower than for non-orphan medicines.
[70] 10 years of the EU Paediatric Regulation (report from the Commission to the European Parliament and the Council (COM(2017) 626, Section 3). Kyle, 2019, Bergmann et al., 2016; Ferrario, 2018
[71] Personalised medicine | European Commission (europa.eu)
[72] Meaning a biological molecule found in blood, other body fluids, or tissues that can be used to follow body processes and diseases in humans and animals. See also: Biomarker | European Medicines Agency (europa.eu).
[73] Section 5 of the Joint Evaluation.
[74] Article 3(1) of the current Orphan Regulation; the criteria for designation should ensure that only products addressing a rare disease fall under the scheme.

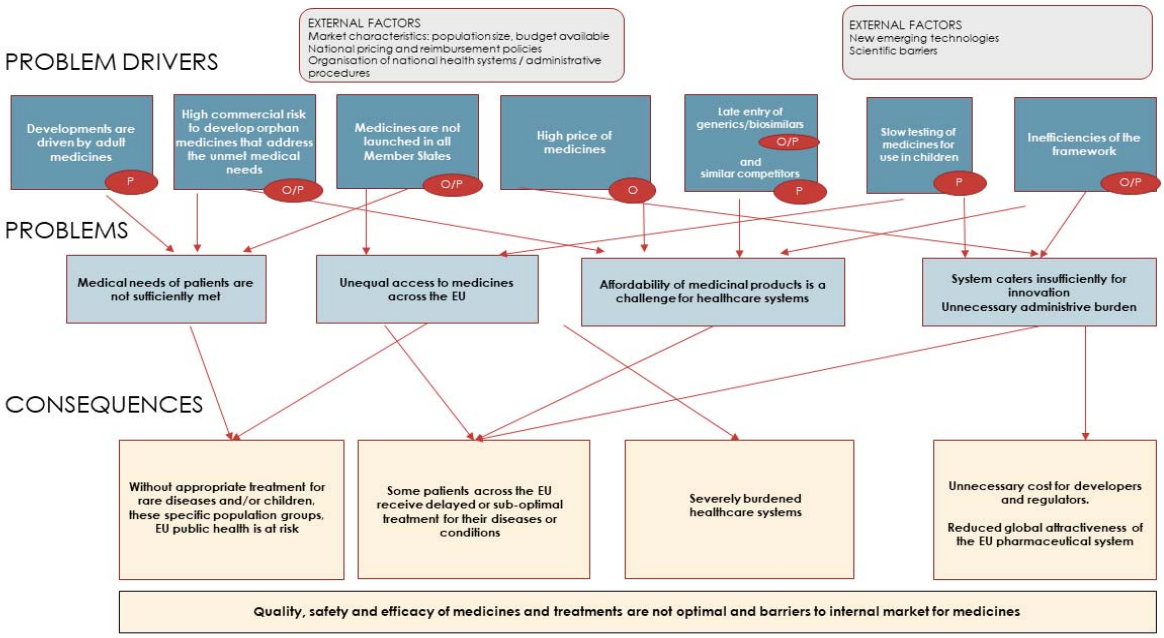
that are exclusive to adults. However, some of those medicines, in view of their mechanism of action[75], may be promising for the treatment of certain diseases in children and therefore should be researched further. This is often the case for anti-cancer medicines. Patient associations and healthcare professionals were specifically concerned about this issue[76].

Concerning **inefficient procedures**, both the Orphan and the Paediatric Regulations rely on certain procedures (e.g. for the orphan designation and the agreement on a PIP) that sometimes proved to be burdensome and inefficient leading to delays in the authorisation of a product[77]. In addition, the paediatric regulation offers 6 months SPC extension for completing PIP, and for orphan medicines 2 years of market exclusivity extension. From the entry into force of the Paediatric Regulation up to 2020, only 11 of these market exclusivity extensions were granted. The system has allowed some companies to game the system: there have been cases where companies have abandoned the orphan status of their product at the moment of marketing authorisation in order to benefit from the 6 months SPC extension. This has created a system which made it difficult for generic producers to know exactly when the paediatric protection would expire and consequently to plan accordingly.

2.2 What are the problem drivers?

Many of the drivers and problems tackled with this initiative are linked with the ones addressed in the review of the general pharmaceutical legislation. Table 1 below presents the interconnections between the drivers, problems and consequences underlying the revision of the general pharmaceutical legislation and the revision of the legislation for rare diseases (O) and children (P):

Table 1: Overview of drivers, problems and consequences[78]



[75] Article 11 of the Paediatric Regulation, provides that the obligation to conduct a PIP is waived when the medicinal product in intended for a disease which only occurs in adults.
[76] See also Annex 2 of this SWD.
[77] Section 5.2.6 of the Joint Evaluation.
[78] Red bubbles indicate the issues which are specific to the revision of the legislation for medicines for children and rare diseases. Only problems relevant for orphan and paediatric medicines are presented in the table.

2.2.1 *Driver 1: Developments are driven by adult medicines*

The paediatric Regulation has been successful to steer paediatric clinical research but as shown into the evaluation, medicines' development remains driven by adult needs. Limited developments are seen in areas where the medical needs of children and adults differ (for example, neonatology and certain types of paediatric cancers).

2.2.2 *Driver 2: High commercial risk to develop and bring to the market new medicines that address unmet medical needs*

Developing medicines for rare diseases and children is often more complex and riskier than for other medicines. Due to their low prevalence, rare diseases face a scarcity of scientific knowledge and clinical trials need to be conducted across several Member States[79]. Moreover, children cannot be considered as a homogeneous group as they cover preterm newborn to adolescents with different physiological characteristics. This results in more complex clinical trials and specific product formulations.

While investment risks and expected financial return may vary significantly, the Regulations only have one set of incentives and rewards[80]. This lack of differentiation does not necessarily direct investments in rare or paediatric diseases where the need is highest. Companies have focused primarily on orphan medicines with the highest expected return on investment and for which science has already evolved, as demonstrated by a clustering in certain diseases. Of all authorised orphan medicines between 2000 and 2017, 72% targeted diseases that have at least one other authorised treatment available[81]. While multiple treatment options can benefit patients and increase competition, development also needs to be directed into areas where there are no authorised treatments at all. Regarding medicines *for children*, it was shown that investments are still smaller when compared to the ones into adult medicines[82]. The constraints and difficulties to fully respect all safety requirements during clinical trials for such small but fragile population may explain this tendency[83].

2.2.3 *Driver 3: Medicines are not launched in all Member States*

The **Orphan Regulation**, like the general pharmaceutical legislation, does not impose any obligation on marketing authorisation holders to launch an authorised product in all Member States nor puts any specific requirements when withdrawing them for commercial reasons[84]. It only allows competitors to break the market exclusivity if they can demonstrate that the orphan product is not delivered in sufficient quantities.Pharmaceutical companies tend to favor the initial launch of the product in a limited number of Member States[85] and begin negotiations with Member States that may grant a higher price and have a higher 'willingness to pay'[86] (often countries with the highest GDP per capita[87]). Furthermore, the timelines for completing pricing and reimbursement decisions and HTA assessment vary considerably between Member States with some being overly delayed[88]

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[79] EURORDIS. Final Conclusions and Recommendations of the Pharmaceutical Forum.
[80] See also Sections 1.2.3 and 1.2.4 of this SWD.
[81] See also Section 6 of the Joint Evaluation.
[82] See also Section 6 of the Joint Evaluation
[83] Vieira I. et al, Paediatric Medicines - Regulatory Drivers, Restraints, Opportunities and Challenges. J Pharm Sci. 2021 Apr;110(4):1545-1556. Available at: https://doi.org/10.1016/j.xphs.2020.12.036.
[84] The number of reimbursed orphan medicines at present varies greatly across the EU. See also: Check et al. (2019), 'A Review of Rare Disease Policies and Orphan Drug Reimbursement Systems in 12 Eurasian Countries', Front Public Health, 2020 Jan 28; 7:416, DOI: 10.3389/fpubh.2019.00416, available at https://pubmed.ncbi.nlm.nih.gov/32117845/.
[85] Section 5.1.2 of the Joint Evaluation.
[86] Meaning the maximum amount of money that may be contributed to receive an extra service or treatment (an important approach in economics for valuation of health benefits and medication programs).
[87] Statistics | Eurostat (europa.eu).
[88] Pharmaceutical Sector Inquiry Final Report – July 2009.

[89]. The recently adopted HTA Regulation, providing for joint assessments may improve the situation, but this also underlines that some problems cannot be addressed by the orphan legislation itself.

The Paediatric Regulation includes very limited provisions to ensure that patients have access to an authorised paediatric medicine. An exception is that when a PIP has led to the authorisation of a paediatric indication for a product already marketed for other indications, such indication has to be placed on the market in the Member States within a two-year period. Furthermore if a company intends to withdraw the medicine which had benefitted from the reward, it has to offer the marketing authorisation to a competitor first. However, access for patients of these products across Member States is not uniform and is influenced by launch decisions of the equivalent medicine for adults. Also, there are currently no tools to influence the launch of adult product under the general pharmaceutical legislation[90].

2.2.4 Drivers 4 and 5: High prices and costs of innovative medicines and delay of entry of generics/biosimilars and similar products

Companies often explain increasing prices of innovative medicines by the increase of R&D costs[91] and small targeted populations are often recalled as a reason for high prices of orphan medicines, even if a recent study found that the clinical costs per approved orphan medicine is lower and in certain cases half that of a non-orphan medicines[92]. Orphan medicines are the source of the fastest growth of the general spending on pharmaceuticals both in the EU and the US[93]. Seen against a growing number of orphan medicinal products on the EU market, limitations in national health budgets have also influenced uptake and patient access[94].

While the new EU Regulation on Health Technology Assessment[95] is expected to improve the situation in terms of speeding up market access through accelerated availability of joint relative efficacy assessments[96], it does not directly tackle any financial burden or necessary changes to national price negotiations and reimbursement models. Those decisions are based on national policies and are outside the scope of EU legislation and this revision[97]. Nevertheless, the regulatory protection periods and the market exclusivity provided by EU legislation give a monopoly power to companies that can influence negotiations and contribute to high prices[98]. Furthermore, the fragmented and non-transparent EU medicines market leads to sometimes significant differences in prices for the same medicine in different countries. The sheer monitoring of the price differences is a challenge in itself, as official list prices do not reflect confidential rebates that can go up to 30-40% of the price[99].

Generics and biosimilars normally reduce the prices. Delayed entry of generics and biosimilars therefore has a negative impact on patient access and affordability. Apart from the small size of the

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[89] See also Annex 2 of this SWD (stakeholder consultation).
[90] Lepola P., Wang S., Tötterman, A.M., et al. (2020). Does the EU's Paediatric Regulation work for new medicines for children in Denmark, Finland, Norway and Sweden? A cross-sectional study, BMJ Paediatrics Open.
[91] OECD, New Health Technologies: Managing Access, Value, and Sustainability, 2017.
[92] Jayasundara K, Hollis A, Krahn M, et al.. Estimating the clinical cost of drug development for orphan versus non-orphan drugs. Orphanet J Rare Dis. (2019) 14:12. 10.1186/s13023-018-0990-4 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
[93] Orphan Drug Report 2022, Evaluate Pharma.
[94] See also Section 2.1 of this SWD.
[95] Regulation (EU) 2021/2282 on health technology assessment (HTA)
[96] Section 6.3.1. of the Commission Impact Assessment 'Strengthening of the EU Cooperation on Health Technology Assessment (HTA)' - SWD(2018) 41 final.
[97] See Section 1 "Policy context" of this SWD.
[98] European pharmaceutical research and development. European Parliament Research Service.
[99] Health at a Glance: Europe 2022 – Pharmaceutical expenditure, OECD

population, there are some additional regulatory hurdles for generic and biosimilar entry due to the design of the Orphan Regulation. Currently, market exclusivity does not allow for generics to *apply* for market authorisation before its expiration, which means an additional windfall protection and delay for generics beyond the 10 years. In some cases a second generation orphan medicine is even blocking generic copies of the first generation product, namely where the first and second generation product were considered similar and as market exclusivity protects against market entry of similar products. Furthermore, new indications in a different orphan disease for an already authorised product lead to a new 10 year market exclusivity period for this indication, meaning that generic/biosimilars cannot copy the entire product but only partially for considerable time[100].

2.2.5 Driver 6: Slow testing of medicines for use in children

The PIPs have to be conducted in parallel with the adult studies, unless the Agency agrees that some or all of the studies with children should be conducted later[101]. Such 'deferrals' are granted for instance if the paediatric studies would delay the 'adult' authorisation or if information deriving from adult studies are needed before initiating paediatric research. Currently over 80% of PIPs include full or partial deferrals, some of them are very long. This results in a delayed access of adapted medicines for children.

2.2.6 Driver 7: Inefficiencies in the legal framework

The development of innovative therapeutic solutions has created some regulatory challenges[102] and this results in the current system not being able to cater for these innovations which could benefits patients with rare diseases and children. Regarding *orphan* medicines, certain scientific developments have challenged established concepts used in the orphan legislation. Current legal definitions are directly linked to the concept of a disease and to the prevalence of the condition. It needs to be verified whether these legal provisions are still fit for purpose in view of new scientific developments[103].

Regarding *paediatric* medicines, the ability to better understand the molecular causes of diseases could allow to identify if certain adult products could be also useful to treat a different paediatric disease. This is particularly relevant in oncology. However, the current Regulation does not allow to explore these potential opportunities, as it waives the obligation for a PIP for products developed for a disease that does not exist in children, thus hampering innovation[104].

Furthermore, for orphan and paediatric products the assessment pathway is currently quite complex. Such products may be assessed by up to four Agency committees: the Committee for Orphan Medicinal Products (COMP) for the orphan designation, the Paediatric Committee (PDCO) for approval of the PIP, the Committee for Medicinal Products for Human Use (CHMP) for the benefit-risk assessment for marketing authorisation and in the case of ATMPs, the Committee for Advanced Therapies (CAT). While the remit of the various committees is clear, inconsistencies of outcomes, data needs and timelines were identified[105]. In addition, orphan designations are granted through a

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[100] These additional market exclusivities means that generic medicines can enter the market in the first indication, but cannot be used in subsequent indications. This indication protection is not as strong as the initial exclusivity, because the doctors and health payers are aware that the generic molecules work the same way in all indications. At the same time, the market exclusivity holder has limited capability to demand a price premium: if the price gap with generics is too large, doctors may prescribe the generic version "off-label" for the protected indication. 16% of orphan medicines currently have multiple orphan indications, and on average they extend the first market exclusivity by 4.2 years.

[101] Article 20 of the Paediatric Regulation.

[102] See also Section 2.1 of this SWD.

[103] Sections 5.3 and 6 of the Joint Evaluation.

[104] Idem.

[105] Idem.

Commission decision, while PIP agreements are directly adopted by the Agency, creating incoherence in pre-authorisation decision-making.

2.3 How likely is the problem to persist and how will the problem evolve?

The Joint Evaluation[106] and the analysis conducted - based on information collected from the Agency and via the consultation process - suggest that the above drivers and problems would continue to exist. While the current Regulations are expected to contribute to an overall *increase* of medicines for rare diseases and for children, this increase is insufficient to rapidly provide treatment solutions for all patients and address unequal access to medicines across the EU. The entry of generic and biosimilar products will remain slow as an application for these products can be submitted only on the day the exclusivity period of the orphan medicine expires. Delayed generic entry will in turn continue to negatively impact affordability of orphan medicines. Some national initiatives, like national orphan plans, try to offer solutions to support rare disease research and product availability on a national level; they have grown substantially since 2009[107] [108]. However, there is no indication that R&D investments will focus more on areas of unmet medical need. Similarly the existing design of the rewards will not prioritise product development in areas of specifically paediatric needs where these differ from the needs of adults. The HTA legislation is expected to provide a positive impact on patient access to new medicines by supporting Member States in taking more evidence-based and timely decisions. A forthcoming revision of the SPC legislation aims to put in place a unitary SPC and/or a centralised procedure for granting national SPCs[109] which is expected to simplify the procedures for obtaining the SPC extension for the completion of the PIPs.

2.4 Megatrends

The persistence of the problem is also confirmed by some of the megatrends identified by the EU Joint Research Centre[110] as part of its foresight activities[111]. Out of the 14 megatrends, four trends are likely to have a strong impact on the aforementioned problems. These trends would also pose additional strain on health systems and research needs and budgets would need to be prioritised between the different challenges.

Megatrend 1 and 4: Shifting health challenges, climate change and environmental degradation. This overarching topic includes trends ranging from the digitalisation of society to demographic changes or environmental challenges. Even though science and technology enable us to live longer, the rise of new diseases due to anthropogenic causes and demographic changes will create a new burden for public health. The Covid-19 crisis best pictures this situation. The impact of changing climate patterns on public health is another example. It is therefore crucial to create a more agile and flexible legislative framework ready to adapt to future challenges and to simultaneously maintain its objectives in terms of research and innovation to ensure development in areas of greatest unmet medical needs and availability and accessibility across Member States.

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[106] Section 6 of the Joint Evaluation.
[107] The EPSCO Council issued a recommendation in 2009 for Member States to create and adopt a plan focused on rare disorders by the end of 2013. Twenty-five Member States followed this recommendation.
[108] Twelve countries (Croatia, Czech Republic, Finland, France, Hungary, Latvia, Luxembourg, Portugal, Romania, Slovak Republic, Slovenia, Spain) have an ongoing national plan/strategy with a specified time-period. Austria, Belgium, Cyprus, Lithuania, and Germany have an 'open-ended' national plan/strategy. In seven countries, the national plan/strategy is expired: Bulgaria (expired in 2013), Denmark (apparently expired 2019), Estonia (expired in 2017), Greece (expired in 2012), Ireland (expired in 2018), Italy (expired in 2016), and the Netherlands (expired in 2018).
[109] Medicinal & plant protection products – single procedure for the granting of SPCs (europa.eu).
[110] The Megatrends Hub, https://knowledge4policy.ec.europa.eu/foresight/tool/megatrends-hub_en#explore.
[111] Foresight is the discipline of exploring, anticipating and shaping the future to help building and using collective intelligence in a structured, and systemic way to anticipate developments. Strategic foresight seeks to embed foresight into EU policy-making. See also: https://ec.europa.eu/info/strategy/strategic-planning/strategic-foresight_en.

Megatrend 2: Accelerating technological change and hyperconnectivity. Increasing technological developments are changing the way we live, but also the nature and speed of new discoveries. In the field of public health, it implicates new ways to generate health data at individual level to develop more personalised treatments based on patients' needs. Technological changes are fundamental in the area of research and innovation to maintain scientific developments, especially in areas where the population affected is small and scattered between several Member States. There are also great potentials in connecting datasets and advanced analytics – in particularly to identify new treatments via mechanism of action research or assess the safety and efficacy of orphan and paediatric medicines based on real world evidence. Administrative burden and inefficient procedures could be improved thanks to the use of technological tools.

Megatrend 3: Increasing demographic imbalances. Global population is growing and age structures more uneven. Especially in Europe, population is ageing and birth rates are declining. Consequently the population of children becomes smaller[112]. This development is expected to make more difficult the organisation of clinical research involving children and would also impact the return on investment for pharmaceutical companies.

3 WHY SHOULD THE EU ACT?

3.1 Legal basis

The Orphan and Paediatric Regulations are based on Articles 114(1) and 168(4)(c) of the Treaty on the Functioning of the European Union (TFEU).[113] These provisions give the EU the mandate to adopt measures which have as their object the establishment and functioning of the internal market (Article 114(1) as well as measures setting high standards of quality and safety of medicinal products (Article 168(4)(c)). Any future legislative proposals, supported by this impact assessment, will be based on Articles 114(1) and 168(4)(c) TFEU. It will also be aligned with Article 35 of the EU Charter of Fundamental Rights that provides that the Union is to ensure a high level of human health protection in the definition and implementation of Union policies.

3.2 Subsidiarity: Necessity of EU action

Diseases do not know borders. Ensuring the availability of medicines for rare diseases and for children affect all Member States. As such, this can effectively be regulated only at EU level. The authorisation of medicinal products, including orphan medicines and medicines for children, is fully harmonised at EU level. Member States cannot introduce specific provisions at national level in this field. A harmonised approach at EU level also provides greater potential for incentivising the development in the area of unmet needs. The market for individual orphan medicines is small even in larger EU Member States. Any national initiative would need to provide substantial incentives for developers to change their investment behaviour. While Member States could offer certain types of incentives, such as tax rebates, few EU countries offered specific financial incentives[114] and they were insufficient. Also, Member States' action to boost paediatric medicines were largely unsuccessful[115].

The legislation respects Member States' exclusive competence in the provision of health services, including pricing and reimbursement policies and decisions as well as prescription of medicines

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[112] The number of children below the age of 16 will have dropped by 14% between 2020 and 2070 (Eurostat 2019 projections).
[113] The Orphan Regulation is only based on the internal market provision, given that the Treaty of Lisbon that introduced additional competences in the field of health (i.e. Article 168 TFEU) did not exist at the time.
[114] Section 5.5 of the Joint Evaluation.
[115] Commission Staff Working Document – Proposal for a Regulation of the European Parliament and of the Council on medicinal products for paediatric use and amending Council Regulation (EC) No 1786/92, Directive 2001/83/EC and Regulation (EC) No 726/2004.

(Article 168(7) of the TFEU). Non-legislative actions at national level described in the Pharmaceutical Strategy for Europe will *complement* the legislative measures that will be proposed in this revision and in the revision of the general pharmaceutical legislation. They relate for instance to mutual learnings and best-practice exchanges in the area of pricing, payment and procurement policies.

3.3 Subsidiarity: Added value of EU action

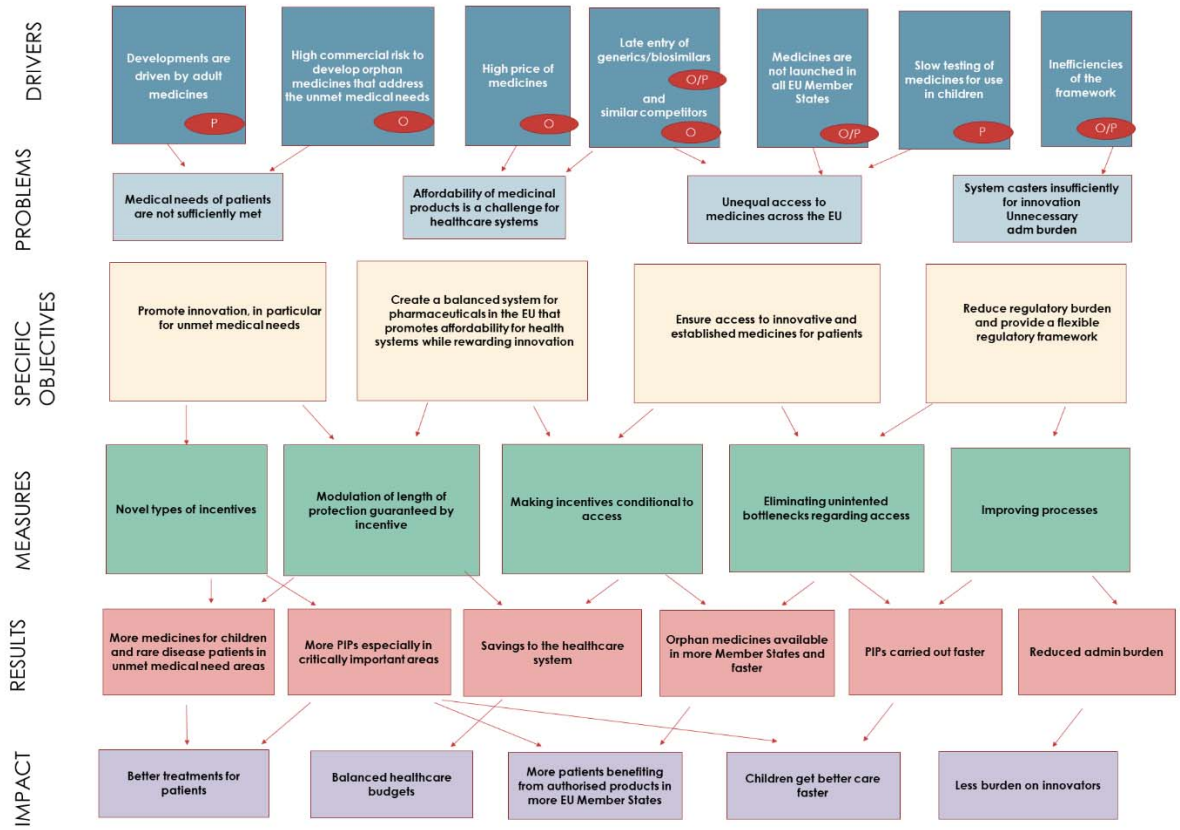
This initiative revises a system with recognised EU added value for the EU patients/citizens, pharmaceutical industry and medicines authorities leading to the authorisation of more medicines addressed to patients suffering from rare diseases and to children. It is expected to bring benefits by addressing unmet medical needs and contributing to reducing unequal patient access to medicines across the EU. At the same time, simplification and streamlining of processes are expected to reduce administrative burden for companies and hence improve the efficiency of the regulatory system. This revision can influence positively the competitive functioning of the market through the review of the incentives and other measures to facilitate entry of generic and biosimilar medicines and hence improve patient access and affordability.

4 OBJECTIVES: WHAT IS TO BE ACHIEVED?

4.1 General objectives

The intervention logic (Table 2) of this initiative builds on the one for the revision of the general legislation[116]. The overall objective of this initiative is to ensure a high level of health protection for all EU citizens and ensure that patients with rare diseases and children have access to high quality medicines and to safe and effective therapies to address their medical needs.

Table 2: Intervention logic



[116] Section 4.1 of the Staff Working Document – Impact assessment on the general pharmaceutical legislation.

4.2 Specific objectives

The revision of the legislations will aim to:

4.2.1 Promote innovation for rare diseases and for children in particular in areas of unmet medical need

Promoting innovation in all areas of rare and paediatric diseases is necessary, as there are still unmet medical needs. This is especially important for medical conditions where there are no treatment options, and for which the health burden is significant for patients suffering from rare diseases (*high* unmet medical needs) and for children. The revision should enable major biomedical research to advance and ensure a pipeline of innovative new medicines. It should also support pharmaceutical R&D and strengthen the competitiveness of the research-based EU pharmaceutical sector.

4.2.2 Create a more balanced system for pharmaceuticals in the EU that promotes affordability for health systems while rewarding innovation

The revision should promote affordability of medicines for health systems across the EU Affordability however should not be promoted at the expense of innovation, which also benefits patients. Thus, the underlying ambition is to create a balance where innovation is rewarded and faster market entry of generic and biosimilar medicines is facilitated, as a means to improve competition across the EU and drive down pharmaceutical costs for health systems.

4.2.3 Ensure timely patient access to orphan and paediatric medicines in all Member States

This objective aims to promote equal access to medicines for all EU citizens, including in smaller Member States. It can only partially be impacted by the pharmaceutical legislation[117]. After a medicine has been developed and authorised, patient access has two dimensions: (i) the equal access to/market entry of innovative medicines across the EU and (ii) continuous supply of all medicines. For this initiative, the focus is on the first dimension (the second being covered by the general pharmaceutical legislation)[118]. To ensure equal patient access across the EU, the aim is to provide a motivation to companies to reach an agreement with Member States more quickly and engage Member States in effective negotiations with the final aim to increase access for patients in more member States. Competition from generic and biosimilars will also serve patient access. Furthermore, a faster completion of paediatric clinical research would make products adapted for children more timely available.

4.2.4 Reduce the regulatory burden and provide a flexible regulatory framework

The revision should increase the attractiveness of the EU regulatory system through simplifying and regulatory requirements and reducing burden for industry and public authorities. The goal is to provide clarity on the regulatory pathways, reduce approval times and costs while maintaining high standards and robust assessment of the quality, safety, and efficacy of medicines. Leveraging digital technology and the use of electronic information could support this objective.

There are synergies between the various objectives, notably objectives 1 and 2 (they both cater for innovation purposes)[119] and between objectives 2 and 3 as more affordable medicines are

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[117] See also Section 2.1 of this SWD.

[118] As regards shortages and keeping products on the market, the aim is to enhance and harmonise notification requirements and obligations in the *general* pharmaceutical legislation to ensure appropriate and continued supply across Member States.

[119] Objectives 1 & 2 (unmet needs and patient access) can be related to Article 35 of the Charter of fundamental rights of the EU, which establishes the right to benefit from medical treatment under the conditions established by national laws

expected to become more accessible to more patients and health systems. On the other hand, some trade-offs between achieving patient access (objective 3) and rewarding innovation (objective 2) may be necessary, depending on market launch of innovative medicines[120]. Trade-offs are also inherent *within* objective 2, i.e. between rewarding innovative medicines and ensuring that medicines are affordable, which is often achieved by means of generic/biosimilar competition. A flexible regulatory framework with less regulatory burden (objective 4) will enable faster translation of innovation into authorised products in synergy with objectives 1+3.

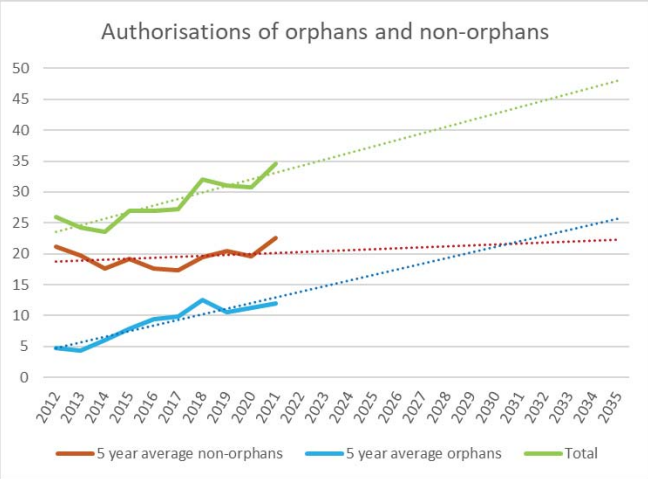
5 WHAT ARE THE AVAILABLE POLICY OPTIONS?

5.1 What is the baseline from which options are assessed?

The baseline is represented by the business-as-usual scenario, meaning the situation where no policy changes are made, with the current Paediatric and Orphan Regulations remaining in force. The revision of the general pharmaceutical legislation is factored into the baseline. The standard level of regulatory data protection will be reduced to 8 years, but medicines addressing unmet medical needs would receive an additional 1-year of protection, and medicines launched in all EU markets would get 1 additional year[121]. The changes due to the revision of the general pharmaceutical legislation are not expected to alter the number of new medicines (both orphan and non-orphan) on a scale that would influence the projections

To see how the **orphan medicines** landscape will evolve in the next 15 years (2020-2035) without any changes to the orphan regulation, a dynamic baseline has been developed against which the impacts of the policy options and common elements have been compared. Figure 1 below projects the number of orphan and non-orphan medicines based on historic EMA data, in line with the projection in the general pharma impact assessment. We expect the approval of 375 orphan medicines in the next 15 years, or an average of 25 orphans per year. Historic EMA data shows that out of the 190 authorised orphan medicines (2000-2020), 24% (or 46 products) targeted diseases that had no alternative treatment options. This is a good proxy for the share of high unmet medical needs, it has been assumed that a 20% share of orphan medicines developed/authorised up to 2035 will address HUMN, i.e. 5 products per year or 75 products in total.

Figure 1 – Number of authorisations for non-orphans and orphans



and practices and a high level of human health protection in the definition and implementation of all the Union's policies and activities.

[120] Often innovative products comes with a high cost which is not affordable by several Member States, reducing therefore the aces for patients.

[121] See also Section 6.1.1 of this SWD.

The increasing trend of orphan medicines will also raise further affordability issues. The average list price of new orphan medicines is expected to continue to increase, and generic competition will not be specifically fostered[122]. Regarding *patient access* to medicines, no major improvement would be expected. The amendment proposed for the length of regulatory protection for the revision of the pharmaceutical legislation would not impact the access for orphan products, as the 10 years market exclusivity protection would make it indifferent for orphan medicines whether they get 8+1 or 9+1 year's protection in the other legislation for launching in all member states. Moreover, the effective period of market exclusivity would continue to be longer than 10 years, as generics/biosimilar can only file after expiry not enter the market thereby delaying generic entry.

For **medicines for children**, EMA data shows that in the last 5 years 60% of new applications were obliged to carry out PIPs and 40% were exempted by a waiver. We expect a similar ratio for the coming years among newly authorised medicines. Therefore, out of the 675[123] new medicines expected to be authorised in the next 15 years, it has been assumed that **405** would have been obliged to carry out paediatric studies. This is not however equivalent to the number of new medicines available to children, as studies may conclude that the medicine is inappropriate for paediatric use. The current procedure for agreeing a PIP, would continue to allow products with the potential to address important unmet medical needs for children (e.g. certain anti-cancer medicines) to escape the obligation[124]. Moreover, more and more innovative products may struggle with the current requirement to present a complete clinical development plan at very early stage of development as such, risking to delay their development and increasing the administrative costs for the PIP procedure. Beyond the obligations, the paediatric regulation rewards timely completion of PIP with a 6-month SPC extension. Some medicines will complete a PIP, but will not benefit from the reward if they do not have an SPC protection (i.e. 50% of new medicines) or if the completion is so late that they cannot claim anymore the extension[125]. Out of the 45 new medicines, 60% will have a PIP obligation and of them 35-40% will be able to redeem the incentive: we expect 10 new SPC extensions annually. Regarding the budgetary impact of the reward, there will be a tangible increase in the number of SPC extensions awarded going from the current four per year[126] on average to ten. The SPC extension will apply to all sales of the product, not just those intended for use in children. The value of the reward and consequently the additional cost for health payers depend on the revenues generated by the rewarded medicine. While the evaluation has shown that on average the SPC has provided a fair reward for conducting PIPs, there are some blockbuster medicines[127] for which a six-month extension means hundreds of millions extra revenue and others for which it brings no extra revenue (those that rely on RP or patent as last line of protection). As for timely access to paediatric use of new adult medicines, the baseline does not offer any improvement. Currently, 86% of PIPs include deferrals, meaning that the completion of the PIPs can be delayed to after the market authorisation for most new medicines. Analyses on the basis of data provided by the Agency demonstrated that the average expected PIP duration was 9.18 years and more than 7 years for around the 70 % of the PIPs.

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[122] See also Section 2.1 of this SWD.

[123] Referring to the projections of the general pharma impact assessment, assuming 40-50 new medicines yearly on average for the next 15 years.

[124] See also Section 2.1 of this SWD.

[125] The extension must be claimed 2 years before SPC expiry the latest.

[126] Currently on average 4 extensions are utilised per year but taking into account the timing necessary to complete a PIP, an increased number of PIPs are foreseen to be concluded in the coming years.

[127] We have noted that out of 12 blockbuster medicines (those that have a revenue of €1 billion per year in the EU market) in a basket of products analysed, 8 had a paediatric extension; see also *F. Schmidt*, Beyond protecting economic interest, SPCs as a tool to support public health goals, EPLR 2018, p. 63.

5.2 Description of the policy options

The different policy options vary as to the incentives or rewards to which orphan and paediatric products would be entitled to. In addition, the revision will include a series of common elements that are present in all the options. Each policy option aims to address all the objectives and all the problems identified. The options are in line with the measures considered in the revision of the general pharmaceutical legislation. The situation in other jurisdictions (notably the US and Japan) has been taken into account (see sections 1.3.3 and Annex 8). A tabular description of the options and a further description of the various elements is provided in Annex 5.

5.2.1 Medicines for rare diseases

The following policy options have been assessed.

- **Option A:** keeps the 10 years of market exclusivity and adds - as an additional incentive - a transferable regulatory protection voucher for products addressing HUMN of patients. Such a voucher allows for a one-year extension in the length of regulatory protection and can be sold to another company and used for a product in that company's portfolio (more details in Annex 4 section 5).
- **Option B:** abolishes the current market exclusivity of 10 years for all orphan medicines.
- **Option C:** provides for a variable duration[128] of market exclusivity of 10, 9 and 5 years, based on the type of orphan medicine i.e. for HUMN, new active substances and well-established use applications, respectively. A 'bonus' market exclusivity extension of 1 year can be granted, based on patient accessibility within 2 years of authorisation in all relevant Member States (that has patients), but only for HUMN products and new active substances.

  Similarly to the concept of the revision of the general pharma legislation, companies could still receive the market launch incentive if, due to reasons beyond their control, the market launch is delayed or missed (e.g. the Member State doesn't wish to be supplied at that particular moment or doesn't have the specialised infrastructure, e.g. in case of ATMPs). The specific situation of **SMEs and not-for-profit entities** and their capacity to engage in multiple parallel pricing negotiations will be taken into account by allowing a 1-year longer period to comply with the market launch conditions.

Regulatory data protection[129] - as provided by the general pharmaceutical legislation - will also apply to orphan medicines.

Elements common to all policy options

- **Stimulate innovation** (to improve research and development especially in areas of (high) unmet medical needs – **objective 1**):
  - Criteria to identify products addressing HUMN will be set in the orphan legislation[130]. Such products would address areas where no treatment is available. The definition of such criteria – in combination with the incentives geared towards medicines addressing HUMN – aim to support the development of these medicines.
  - Products addressing HUMN will be **entitled to increased scientific support by the Agency**[131]. The enhanced interaction with developers of promising medicines for

[128] As regards the international outlook, important comparators like the US and Japan provide 7 and 10 years of market exclusivity, respectively. The tested durations were selected to ensure coherency with the selected length of the regulatory protection under the proposed preferred option of the revision of the general pharmaceutical legislation.
[129] See also Section 1.2.3. of this SWD.
[130] See Annex 9 for the criteria considered.
[131] E.g., scientific advice, PRIME, rolling review.

HUMN will optimise their development plans and speed up evaluation so these medicines can reach patients earlier.

- **Faster generic/biosimilar competition** (to improve affordability and patient access – **(objectives 2&3**):
    - Generics/biosimilars can enter the market **at day-1** of the expiry of the exclusivity period[132] by allowing the filing of an application prior to expiry. This will align the regime for generics with the one of the general pharmaceutical legislation.
    - Reduction of **consecutive periods of market exclusivity** for new indications of the same orphan medicine by introducing them under the same "Global Marketing Authorisation" (GMA). To ensure that both new indications are developed and that possible multiple and consecutive extensions of a full market exclusivity duration are reduced (the latter with negative consequences for affordability), the second and third indication authorised will be rewarded with a 1-year extension each of the overall market exclusivity period[133]. This will limit consecutive durations of the market exclusivity and is therefore especially intended to support affordability, as it will lead to shorter durations of market exclusivity and faster generic/biosimilar competition.
    - The market exclusivity **granted to a second generation product that is similar** to the first generation product will not be applied in respect of generic products of the first reference product for which the market exclusivity expired[134]**.** This will avoid evergreening[135] [136].
    - **Encourage companies that lose the commercial interest in an orphan medicine to offer it for transfer to another company** rather than withdrawing it. This is intended to improve patient access as more products will remain on the market[137].
    - **The duration of the orphan designation** (assigned early in the development of a product and prior to obtaining a marketing authorisation) will be **capped** for newly designated orphan medicinal products at 7 years (there is no limit today) to stimulate timely product development[138]. These measures are intended to ensure an increase in availability and timely access of patients.
- **Reduce the regulatory burden and provide a flexible regulatory framework (objective 4):**
    - **Provide for the possibility to adapt the current definition of an orphan condition** to ensure that the legislation is 'fit' to embrace technological and scientific

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[132] Currently, a marketing authorisation dossier can only be submitted at the end of the marketing authorisation period.

[133] This additional market exclusivity would apply to the product itself, not just to the specific indication. This implies a maximum of 12 years of total market exclusivity to various orphan indications related to one product.

[134] Section 5.2.3 of the Joint Evaluation.

[135] Second, independent periods of market exclusivity were contested in Case T-140/12. "Evergreening" strategies extend the effective protection period and thus allow pharmaceutical companies to maintain a market share after their protections expire by introducing "follow-on drugs" - those with slight changes made to them after expired protections that would normally allow generic competitors to enter the market.

[136] It will therefore address an unintended consequence of the current orphan legislation, namely that currently it is possible for an originator to obtain market exclusivity for a second generation product that is *similar* to the first generation product (thereby preventing swift generic/biosimilar competition).

[137] The Joint Evaluation (Section 5.1) found that 11 authorised orphan medicinal products were withdrawn (between 2000 and 2017). If the companies of these products can be encouraged to offer it for transfer, this would improve overall timely authorisation of orphan medicinal products and patient access across Member States. A transfer of the marketing authorisation can be done under Regulation (EC) No 2141/96 free of charge.

[138] The Joint Evaluation (Section 6) concluded that this transformation from concept to an authorised orphan medicine remains slow. Capping the orphan designation could lead to expiry of some of those designations, but may also encourage companies to quicker advance the authorisation process. In view of the average time of 5 years between designation and authorisation, a 'cap' of 7 years provides a buffer factoring in potential longer development timelines in individual cases; such cap should lead to a few extra products being developed.

advances[139]. This is intended to support the development of products in HUMN areas (objective 1) and to cater for efficient procedures for designation and authorisation.
- **The orphan designation criterion[140] on the basis of return on investment** will be abolished, since it has never been used[141].
- **Responsibility for adopting decisions on 'orphan designations'** will be transferred from the Commission to the Agency. These measures are intended to provide more effective and efficient procedures.

5.2.2 Medicines for children

The following policy options have been assessed. They all include the common elements and differentiate by changes to the system of rewards provided to developers of medicines.

- **Option A**: the 6 months SPC extension is kept for all medicinal products. Furthermore, an extra reward benefiting products addressing UMN of children is added (criteria to identify these products will be defined in legislation). This will consist of: either 12 extra months of SPC extension; or a regulatory protection voucher (duration 1 year) which could be transferred to another product (possibly of another company) against payment, allowing the receiving product to benefit from extended data protection (+ 1 year). This would aim to boost the development of products of addressing unmet medical needs of children.
- **Option B**: the reward for the completion of a PIP is abolished. Developers of every new medicine would continue to be obliged to agree with the Agency and conduct a PIP but the extra costs incurred would not be rewarded. As today the SPC extension comes at a cost to health systems, with impact also on accessibility for patients, the elimination of the reward would contribute to ensure an early entry of generic products and therefore reduce the financial impact on health systems and in parallel facilitate access for more patients.
- **Option C**: The 6 months SPC extension remains the main reward for the PIP completion.

Elements common to all policy options:

- Criteria to identify products which have the potential to address **unmet medical need of children** will be defined in the general pharmaceutical legislation[142]. Products which respond to these criteria will be entitled to **increased scientific support[143] by the Agency** in the early phases of development (**objective 1**).
- The **procedure for setting out a PIP** will be **streamlined and simplified** to better reflect how medicines are developed. The new system will allow for a dynamic plan on the basis of the clinical results obtained (evolutionary PIP). This allows to better accommodate innovation (**objective 1**), a quicker completion of the PIP and faster authorisation (**objective 3**) reducing administrative burden for companies also for PUMA products (**objective 4**).

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[139] If need be, delegated acts to facilitate the adaptation of the orphan condition concept to scientific and technological progress can be foreseen, for instance to avoid that the concept of personalised medicine would make every medicine an orphan. Current Guidelines can continue to ensure that the regulatory framework is not improperly used leading to orphan designations for artificial subsets of common diseases.
[140] The designation criterion of insufficient return on investment (Article 3 (1a) of the current Orphan Regulation).
[141] Section 5.1 of the Joint Evaluation.
[142] See also Annex 9 for the criteria to be considered.
[143] The scientific support by the Agency provides targeted, product and development-stage specific advice from experts to increase likelihood for authorisation. This is different to the financial support in form of grants potentially provided by Horizon Europe.

- **The length of deferrals** will be capped to 5 years[144], so that products reach children quicker than today (**objective 3**).
- **Mechanism of action of a product**. Products which, on the basis of scientific evidence on the mechanism of action, could be effective against a different disease in children[145], have to perform a PIP. This will favour the development of products addressing unmet needs of children (**objective 1**). A similar obligation on the basis of the mechanism of action already exists in the US[146] and would thus align the legal frameworks
- **Abolishing the market exclusivity extension** for completing PIPs would allow predictability for generic products and faster entry of generics **(objective 2 and 3).**

5.3 Options discarded at an early stage

For *paediatric* medicines, the possibility to create lists of unmet needs for children has been discarded. Such possibility has received limited support from all stakeholders. Furthermore, an inventory of therapeutic needs for children is already foreseen by the current Regulation. Such inventory has not be useful to steer development of new products and has been challenging to be kept updated by the Agency. While academics and patients mentioned the need to have multistakeholders consultation to discuss about prioritisation in the development of medicines, such activities are already taken place under the EMA/Commission action plan and do not need any legal revision to continue[147]. There have not been any options discarded for orphan medicinal products.

6 WHAT ARE THE IMPACTS OF THE POLICY OPTIONS?

This section includes an analysis of the main economic and social impacts of the policy measures in the different policy options. The analysis focuses first on the impacts of measures concerning orphan medicines, then paediatric medicines. Finally, it analyses some impacts which are relevant for both. The impacts of the options were assessed in an iterative process, taking into consideration (public and targeted) consultations with stakeholders, literature review, and quantitative analysis where possible. Details of the methodology are available in Annex 4, and a summary of stakeholders' views in Annex 2.

6.1 Medicines for rare diseases

The economic impacts of the policy options on the main stakeholders (industry, public authorities, patients) has been assessed and quantified by focusing on: a) assessing the potential effects of changes to the extension of the Market Exclusivity under the various options (including the introduction of a novel reward under option A); b) assessing the impact of the common elements. Other economic impacts have been considered and they are detailed here below by stakeholder group

6.1.1 Economic impacts of the policy options

Health systems/payers derive benefits in the form of savings from avoided hospitalisation and avoided outpatient treatments due to the number of (HUMN) products authorised for use in patients

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[144] The length of the derogation has been assessed taking into account the average length of PIP with and without deferrals. More information can be found in Annex 4, section 7.
[145] During the consultation activities this was supported by academia and civil society respondents. Industry was initially opposing this measure, their position has however evolved and they are also now supporting it.
[146] See Race The Children Act and https://www.kidsvcancer.org/race-for-children-act/. The Agency is collaborating with FDA in setting up non exhaustive lists of known mechanism of actions. However, as in the US it will be the responsibility of each company to indicate, when applying for a waiver the non-existence of relevant mechanism of action for their products.
[147] Joint action plan to support the development of medicines for children in Europe.

suffering from a rare disease. Costs mainly elate to the extra year of market exclusivity for HUMN and access, and the subsequent delay in entry of generics/biosimilars[148].

Patients' costs and benefits derive from delayed/faster access to the products developed, in particular in areas of HUMN. Other impact on patients are assessed in the social impact section.

Originators will benefit from simplified regulatory procedures and more gross profit from the sales of new (HUMN) orphan medicines. Costs mainly relate to gross profit loss due to the access incentive conditionality and faster entry of generics/biosimilars after the expiry of the market exclusivity. In particular, SMEs will benefit considerably from simplified procedures and scientific support by the Agency. The **generic industry** will also benefit from simplified procedures and more gross profit due to a predictable and earlier market entry when originators do not comply with the market launch conditionality. Costs mainly relate to longer protected sales of (HUMN) originators' orphan medicines.

Which medicines are affected by changes in market exclusivity?

Market exclusivity (ME) is the main feature of the Orphan Regulation, providing a form of protection from generic/biosimilar competition with distinctive characteristics[149].The main variable of the different policy options is the length and conditions of this incentive. However, ME does not play in isolation: the regulatory data and market protection (RDP) granted by the general pharmaceutical legislation and other IP incentives, notably patents and SPCs, also protect against generic competition. While the current ME (10 years with a maximum of 12 years if a paediatric research and development programme is completed[150]) and RDP protection (10 years) start from marketing authorisation, the patent (20 years) and SPC (5-year extension of primary patent - maximum 15 years from marketing authorisation) is counted from patent filing, many years before market authorisation. Depending on the time elapsed between patent filing and authorisation, and whether the medicine is orphan or not, one of these four protections will last for the longest period[151]. Table 3 presents orphan medicines that lose their last protection between 2016 and 2024, based on the type and length of last layer of protection to expire.

Table 3: Length and type of protection of orphan medicines

	Years of protection after market authorisation											
Last line of protection	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19+**	**Grand Total (years)**	**Avg peak annual sales[152]**
Market Exclusivity	10		4								**14**	€ 41.4 m
SPC			2			4	2				**8**	€ 475.8 m
Patent						1	1	1	1		**4**	€ 248.0 m
Grand Total	10		6			5	3	1	1		**26**	€ 206.8 m

Source: IQVIA

[148] The *societal* costs of a disease are considered to be wider than those borne by healthcare systems. The non-healthcare costs of a disease are the use of social services; the costs of involvement of carers; and productivity losses resulting from unplanned absences from work or early retirement by patients (or carers). However, any wider societal impact could not be established at the level of the Orphan Regulation. See also Section 5.2 of the Joint Evaluation.

[149] For a full description of market exclusivity see Section 1.2.2.

[150] See Section 1.2.4 of this SWD.

[151] Copenhagen Economics - Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe (2018)

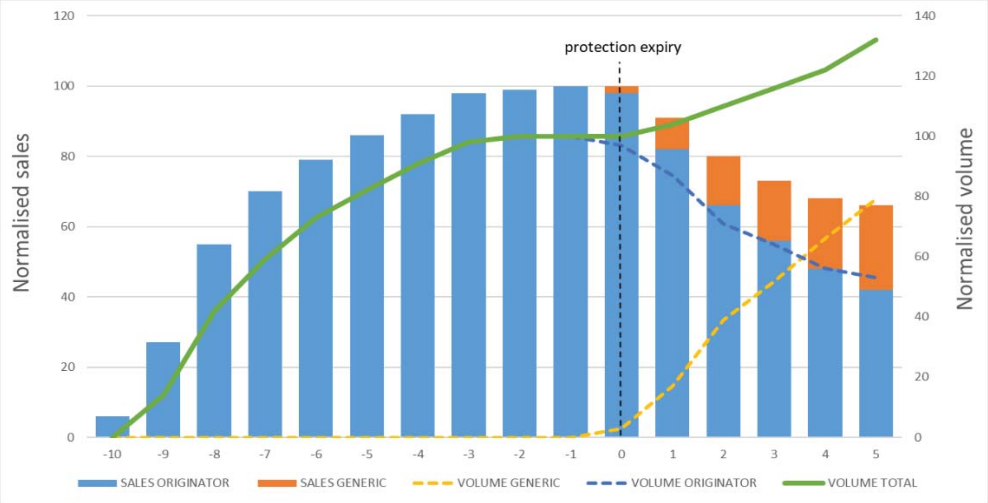
[152] Annual revenue of the medicine in its best-selling year over its lifetime (usually the last year before protection expiry).

ME is the last layer of protection for about half of the medicines (14 of 26) offering either 10 or 12 years of protection. For the remaining other half of medicines, SPC and patent are the last layer of protection, in most cases 15 years or more. These medicines generate much higher revenues on average than the ME-reliant medicines. **Thus, changes to market exclusivity are expected to affect around 50% of orphan medicines in practice with far lower revenues than the average.** Thus, out of the 25 orphan medicines that we expect to be authorised annually 15 years from now, it is expected that half, i.e. 12-13, will be reliant on market exclusivity as last line of protection. Out of these, around 20% (or 2-3 products) will address HUMN (see also Section 5.1).

How market exclusivity protection generates value/cost for stakeholders

To calculate benefits and costs deriving from market exclusivity, the analysis relied on the conceptual model presented in the revision of the general pharmaceutical legislation impact assessment, which follows the lifecycle of a representative innovative medicine (Annex 7, sections 3 and 3.b)). This analogue in Figure 2 below is extracted from analysing historical sales data of innovative medicines and their generic competitors before and after protection expiry[153]. During market protection period, innovators can enjoy high monopoly revenues. Once the protection expires, the generic medicines enter the market with a lower price, carve out a growing market share and force the originator to offer discounts[154]. The volume of generic medicines steeply increases, partly because some users substitute the originator medicine with generics and partly because the total volume rises with increased affordability. For health systems, the price drop following generic competition means cost savings. Extending the protection allow innovators to seek longer monopoly rents, but it delays cost savings and broader access for the public and delays revenues for generic companies. Decreasing protection has the exact reverse effect.

Figure 2: Normalised sales and volumes of originator and generic products



The analogue allows to measure economic impact of the change for the different stakeholders, however the unit of measurement is different for the various stakeholders:

- For **health payers** we measure the impact of changes by the change in the **cost of medicines**, which can be directly deducted from the total sales of originator and generic medicines in the IQVIA data.

[153] Description of the methodology and analogues is further elaborated in Annex 4 (sub-sections 1.1, 1.2 and 1.3) of this SWD.

[154] The evaluation of the generic pharma legislation found that originator products can maintain a 30% premium over their generic competitors.

- For **patients**, we measure the impact of change by the change in the **volume of medicines**. The more/less the volume, the more/less patients could benefit from therapy, either using the originator or the generic product. We present the volume change in a monetised form, by showing the monetary value of the additional or lost volume of medicines. In the analysis we refer to this as *"Δ of patients treated (monetised)"*.
- For **originator** and **generic industry,** the key measure of impact is **the gross profit** that they can realise from their business operations. Gross profits are calculated by subtracting estimated manufacturing and distribution costs from revenues according to the methodology set out in Annex 4.

We have the tools to monetise the direct economic impacts of the incentives. However, the incentives serve a purpose, e.g. they stimulate development of therapies for unmet medical needs, enable faster and broader patient access. **Monetising these societal benefits has practical and ethical challenges**: there is a large variation among medicines' value, influenced by the patient population, the nature and severity of disease, etc. Moreover, monetising the social benefits requires putting a monetary value on patients' life and health, as well as on the physical and emotional burden of their families and carers. We thus have chosen not to monetise these impacts, rather quantify them as much as possible, explain them in the text, and highlight them in the summary cost-benefit tables.

Option A – keep market exclusivity unchanged and add a novel incentive

Retaining the 10 years market exclusivity does not have an economic impact on the orphans compared to the baseline. However, the 10-year protection, granted regardless whether the product is launched in all EU countries or not, would neutralise the access incentive of the general pharma legislation for what concerns orphan medicines (see Table 4 below).

Table 4: Length of regulatory protection and market exclusivity in Option A

Option A	Regulatory protection	Market exclusivity	Last layer of protection	ME added value
Orphan medicines launched in all EU	9 (8+1)	10	ME	+1 year
Orphans NOT launched in all EU	8	10	ME	+ 2 years

.

Option A also introduces **a novel incentive** for products addressing HUMN, namely *transferrable exclusivity vouchers*. Such a voucher could be used to extend the protection of another medicine of the developer, or the developer can sell the voucher to another company (transferable), which then can use it for a medicine in its own portfolio, likely a blockbuster.

The impact assessment on the revision of the *general* pharmaceutical legislation[155] discusses the case for using such an incentive for the development of novel antimicrobials. It has been argued, in particular by the pharmaceutical industry[156], that orphan medicinal products are also a good candidate for a novel incentive, like the vouchers, given that they serve small populations and the profits that they promise to generate may not direct sufficient resources to their development.

However, rare disease medicines have become more important revenue generators[157] and, moreover, a transferable exclusivity voucher would be ill-suited as an incentive to promote investment in HUMN products for rare diseases. This is because the number of vouchers would inevitably become

[155] Staff Working Document – Impact assessment on the general pharmaceutical legislation (Section 6).
[156] See also Annex 2: stakeholder consultation (synopsis report).
[157] As explained above under 'baseline scenario' in Section 6 of this SWD.

too high (considerably higher than in the case of antimicrobials) and their power as an incentive would thereby be severely undermined. This would also nullify the value of vouchers as an incentive for novel antimicrobials. This consideration applies *a fortiori* to medicines addressing an unmet need for children, given that the number would be even higher and the case for an inability of these products to generate revenue is even weaker.

A voucher operates as an incentive, because it confers a rent on the voucher holder. An economic rent is a revenue that accrues on the basis of ownership of a limited asset or resource without requiring commensurate risk or effort[158]. The value of such a rent-generating asset resides in its rarity. When vouchers becomes less rare, the rent associated with all vouchers is diminished. The analysis below, which is developed further in Annex 4, uses real world data to estimate the rate at this occurs, i.e. the nature of the inverse relationship between the size of the rent and the number of values issued.

It is estimated that there will be 3-6 HUMN medicines for rare diseases per year and this will entail competition among voucher sellers that will ensure that by far the larger share of the rent associated with the voucher accrues to the voucher *buyer*. This rent, which comes at a high cost for payers, is a by-product of the rewards for pharmaceutical companies with the highest revenue-generating medicines and does not contribute to the intended incentive[159]. **Figure 3** models two scenarios, one with three HUMN medicines per year and one with six and demonstrates how the benefits of the incentive are shared among the voucher buyers and sellers in the two cases. The green and orange bars are the RDP-protected products from the annual cohort for which a voucher is bought, with the value of the voucher split between buyer rent and seller rent. The yellow bars are the RDP-protected products for which no voucher is bought (Annex 7, section 5).

Figure 3 – the seller and buyer share of voucher rent varies with the number of vouchers

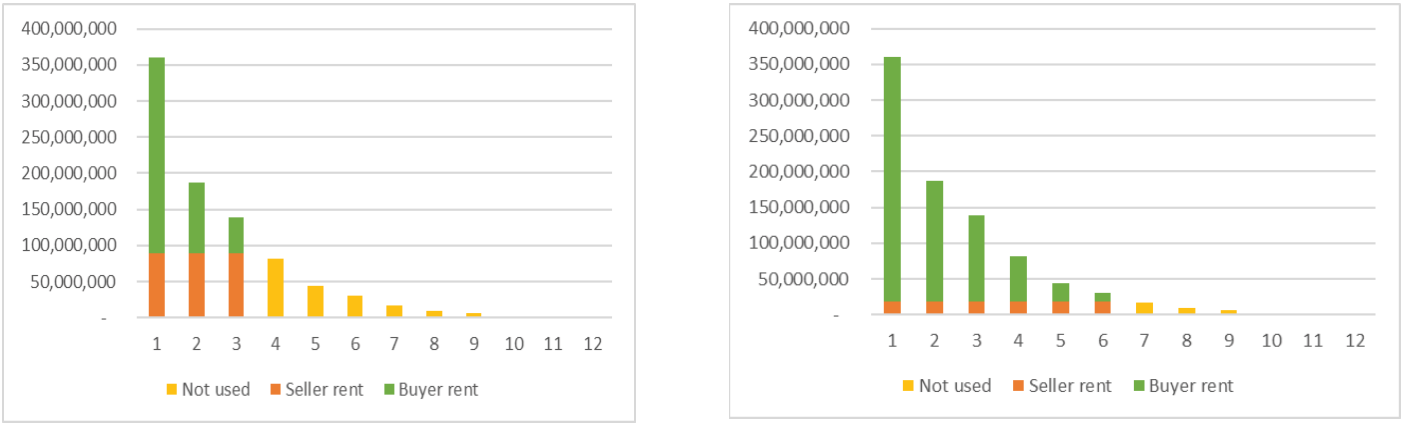


Table 5 – economic impact of the voucher	Systemic change (5 HUMN/year)
Gross profit of HUMN developer	**+€151m**
Gross profit of voucher buyers	+€576m

[158] Economic rents | UCL Institute for Innovation and Public Purpose - UCL – University College London

[159] With the exception of the small minority of products that enjoy an additional year of protection thanks to an additional indication under the current regime, these products were authorised 10 years before their protection expired, so the sample comprises those medicines that were authorised in the period 2004-2014.

Generics gross profit	-€122m
Cost to public payer	**+€639m**
Δ of patients treated (monetised)	--€355m
Patients + payer gain/loss	**-€994m**

With three vouchers issued a year, the seller's rent is already less than the buyer's share at 39%. With six, it is only 13%, with the remaining 87% captured by companies that are not the intended beneficiaries of the scheme.

Table 5 summarises the economic impacts of the incentive on the different stakeholders, if 5 HUMN medicines for rare diseases per year are awarded (in line with the assumptions presented in the baseline). The direct cost to the public payer is around €639m, and if we take into account unserved patients due to retained high prices, **a billion euros loss to the public** is expected, and only a small fraction of it (€151m) would benefit the 5 developers, €30m each. It is estimated that the incentive would induce around 5 more HUMN addressing orphan medicines over 15 years.

Option B – no market exclusivity

Option B proposes the complete **elimination of market exclusivity** in an attempt to address affordability and the high cost of orphan medicines. However, the orphan medicines would not lose 10 years of protection, because the revised regime for regulatory data protection[160] also provides an 8- or 9-year[161] protection for all medicines, including orphans (Table 6).

Table 6: Length of regulatory protection and market exclusivity in Option B

	Regulatory protection	Market exclusivity	Last layer of protection	Change to baseline
Orphan medicines launched in all EU	9 (8+1)	0	RP	-1 year
Orphans NOT launched in all EU	8	0	RP	-2 years

Option B would result in a 1-year protection loss for orphan medicines that are launched in all EU countries and a 2-year loss for those that are not, because of the revised regulatory protection in general pharma. In accordance with baseline projections, we expect 10 orphan medicines annually where the market exclusivity is the last layer of protection of these, we expect that 4 would comply with market launch in all Member States and 6 would not.

With these input variables our model in Annex 4 (section 3.c.i) leads to the following results per stakeholder (see Table 7).

Table 7 – economic impact of no market exclusivity in combination with changes of regulatory protection

	Product level change 1 year loss	Product level change 2 years loss	Systemic change (4 all-EU launch, 6 not all-EU)
Originator gross profit	**-€47m**	**-€94m**	**-€751m**
Generic gross profit	**+€6m**	**+€13m**	**+€101m**
Cost to public payer	-€27m	-€54m	-€430m
Δ of patients treated (monetised)	+€21m	+€35m	+€295m
Patients + payer monetised gain/loss	**+€48m**	**+€89m**	**+€725m**

[160] This change will derive from the revision of the general pharmaceutical legislation.
[161] If the market launch conditionality is fulfilled.

Option B would generate an annual €430m savings to public payers, and with the additional patients served thanks to earlier price competition, the public saving amounts to €725m a year (over the annual €40-50bn that the EU spends on orphan medicines). Apart from supporting affordability, this option also contributes to improving access by allowing the incentive introduced in the general pharmaceutical legislation to affect orphan medicines.

For developers of orphan medicines, the direct impact of abolishing the incentive would be €751m in lost profits. This impact would be amplified by the message transmitted to patients, researchers, companies and investors active in the rare disease area. Divestments and shifting research priorities would likely withdraw resources from orphan medicines development and would be negatively perceived by all stakeholders.

Option C – modulation of market exclusivity to match regulatory protection[162].

Table 8: Length of regulatory protection and market exclusivity in Option C

	Regulatory protection	Market exclusivity	Last layer of protection	Change to baseline
Orphan medicines launched in all EU	9 (8+1)	10	ME	0 year
HUMN orphans launched in all EU	9 (8+1)	11	ME	+1 year
Orphans NOT in all EU	8	9	ME	-1 year
HUMN orphans NOT in all EU	8	10	ME	0 year
Well-established use orphans	0	5	ME	-5 years

+1 year for HUMN addressing orphan medicines

To demonstrate the impacts of **1 year protection extension for medicines addressing HUMN**, we again use the analogue elaborated in Annex 4 (section 3.d). In accordance with baseline projections, we expect that from the 10 orphan medicines annually where the market exclusivity is the last layer of protection, 20% or two products **would address HUMN** and therefore be eligible for the extra year.

Table 9 – Impact of change of +1 year market exclusivity protection

	Product level change	% change	Systemic change (2 medicines)
Originator gross profit	**+€47m**	**+7.7%**	**+€94m**
Generic gross profit	-€6.5m	-28%	-€13m
Cost to public payer	**+€27m**	**-2.9%**	**+€54m**
Δ of patients treated (monetised)	**-€14m**	-2.4%	**-€28m**
Patients + payer monetised gain/loss	**-€41m**	**-4.3%**	**-€82m**

[162] It follows the general pharma legislation by offering a lower, 9 years market exclusivity as a default, which can be extended by 1 year if the medicine is launched in all EU markets. Furthermore, products addressing HUMN would be granted a market exclusivity extension of 1 year (i.e. 10 years as a default for HUMN products).

We estimate that **an average orphan medicine addressing HUMN** and relying on market exclusivity as last line of protection **will be able to generate €47m more profit** (or 7.7% more than in baseline). Such medicines will become more attractive commercially for developers, and their proportion among the newly authorised medicines would increase. We estimate that instead of the 75 projected HUMN addressing orphan medicines in the dynamic baseline (Section 5.1), there would be 80-85 HUMN products authorised in the next 15 years.

The cost of a +1 year protection for HUMN protection would be shared among generic industry, health payers and patients. With 2 of such incentives annually, the generic industry would lose €38m in revenues a year, which translates into €13m decrease in gross profits. The **health payers would need to pay €54m more on an annual basis**. The model also accounts for the patients that would not be served due to the higher prices that result from extended protection. Accounting for that effect too, the **cost for the public would rise by €82m annually**. In exchange for this public cost, the HUMN incentive would directly reward investment in HUMN R&D and likely would have a spill-over effect by sending a signal about the importance of HUMN orphan medicines[163].

Access conditionality

Option C offers the same market exclusivity period for standard orphan medicines as the baseline, 10 years, but only if the medicine is launched in all EU markets within 2 years of authorisation. If not launched in all markets, the protection period is 9 years. This aims to motivate companies to launch in all EU member states, and not to leave out small markets, which are not attractive enough commercially. Similarly to the general pharma revision, it is expected that some medicines will not comply with the access incentive conditions. Given the lower level of baseline compliance with the proposed conditionality of orphan medicines reliant on ME compared to non-orphan medicines reliant on RP, the gap to be bridged will be larger. The assumption is therefore made that 40% of orphan medicines will comply (for non-orphans it is 50%[164]), and 60% will not. Thus, of the 10 orphan medicines expected to have ME as last line of protection, we expect that 4 would comply with market launch in all Member States (and 6 not).

If a standard orphan medicine is **launched in all EU member-states**, the reward will have the same economic impact as in the baseline, with the 10-year market exclusivity protection.

No distinction is made here between HUMN and non-HUMN ME-reliant orphan medicines (the total of 10 includes both), since in either case, the length of protection will be increased by one year if the access conditionality is met as compared with those that do not comply. The table below therefore accounts for both cases, using the model from Annex 4 (section 3.c.ii and section 6):

	Product level change	% change	Systemic change (6 medicines)
Originator gross profit	**-€47m**	**-7.7%**	**-€282m**
Generic gross profit	+€6m	+28%	+€38m
Cost to public payer	**-€27m**	**+2.9%**	**-€162m**
Δ of patients treated (monetised)	+€21m	+2.4%	+€126m
Patients + payer monetised gain/loss	+€48m	+5.0%	**+€288m**

[163] It is expected that national and EU-level research funding programmes would follow suit, and channel resources specifically to HUMN addressing innovation. National pricing and reimbursement systems could also differentiate the HUMN addressing orphans, making marketing conditions more beneficial to them. The same spill-over affects across the ecosystem were visible following the adoption of the orphan regulation, bearing its fruits 10-20 years later.
[164] General pharma IA SWD, Section 8.1.

Table 10 – Impact of change of -1 year market exclusivity in case of non-launch in all MS

For the public payer/patient this instrument is a win-win, if medicines comply, timely access across the EU will increase, and if not, the protection period decreases, lowering cost for society by 48m. The decreased protection translates to 47m lower gross profit per medicine, or 282m for the whole innovative industry and to 38m higher profit for the generic industry. These impacts show only the direct economic impact of the *incentive*. However, there is an expected and non-monetised **positive societal impact**, in the form of **faster, increased and more equitable access** across the EU.

Well-established medicines

Option C also replaces the current additional 10 years with 5 years of market exclusivity protection for **well-established use medicines**, those that have already lost their other protections and for which generic versions exist. Products authorised through this 'route' have attracted substantial scrutiny because of cases in which producers substantially increased the price once the market exclusivity was granted for the newly-authorised medicine that was previously available to patients at a far lower price as a magistral formula or in the form of hospital preparation[165]. The shorter duration still rewards the effort to obtain a marketing authorisation and comply with the high safety and quality standards of an authorised product but reflects that these established medicines have encountered less development risks. It also addresses to a certain extent prolonged price hikes.

The adoption the orphan regulation offered the opportunity for companies to "orphanise" old medicines and many seized the opportunity. By now such low-hanging fruits are harvested and we expect only a few (2-3) well-established use market exclusivities granted per year in the future. Given the low frequency and little value of protection (protection only in a rare indication with co-existing generics), the economic impacts are insignificant in comparison to the other measures.

Stakeholder views

No stakeholder group asked to abolish the market exclusivity, which is the current main incentive (market exclusivity) that fosters developments in the area of orphan medicinal products. It has been suggested that such measure would send a negative signal to patients, researchers and developers and would undermine several efforts the EU does in research and innovation (Horizon Europe) and for rare disease patients (European Reference Networks).

Most stakeholder groups agreed that a revision of the current incentive system is needed (although pharmaceutical industry wanted more) by creating a connection between incentives and obligations. A *variable* duration of the market exclusivity (**Option C**) would answer respondents' concerns that the current 'one-size-fits-all' incentive framework is not sustainable for national healthcare systems. It will also better take into account the focus on product development for greatest patient needs and the costs of development for the product. Health payers and public authorities[166] emphasised that

[165] Leadiant® gained an orphan designation in 2014 and a marketing authorisation in 2017 for the treatment of cerebrotendinous xanthomatosism. Before the market entry of Leadiant®, patients with cerebrotendinous xanthomatosis were treated with off-label drugs with the same active ingredient, at a very low cost per patient. From 2017 towards the end of 2020, the average price of Leadiant® suddenly excessively increased. National competition authorities in the Netherlands, Italy and Spain undertook proceedings about Leadiant's excessive price increase and found it disproportionate as the orphan medicine was not 'innovative' and not requiring substantial investments in the development. See also: ACM imposes fine on drug manufacturer Leadiant for CDCA's excessive price | ACM.nl

[166] Public authorities favour a market exclusivity with a shorter initial duration in cases where the development effort is simpler as it has been based on known off-label treatments. This would be taken on-board under Option C, allowing for earlier market entry of (similar) competitor products in case of orphan medicines that are authorised on the basis of bibliographical data (well-established use) or not falling in the category of HUMN.

rewards and incentives should be *differentiated* and highest incentives should be concentrated mainly on areas where no treatment options are available.

Impacts of the common elements to all options

Allowing entry of generic medicines as soon as market exclusivity is expired, means that an **application for authorisation** of a generic version of the medicine **can be submitted** during the protection period, and can enter the market right after expiry of the market exclusivity. Currently, generic versions of orphan medicines cannot start the authorisation process before the market exclusivity expires[167]. This creates a windfall protection of at least 9 months beyond the 10 years ME, equal to the time needed to authorise a generic medicine from submission[168]. It is estimated that 10 out of the expected 25 new orphan medicines would be impacted per year, the ones where ME is the last layer of protection. Apart from legal certainty for generics it would mean up to €360m savings to the public. Originators would lose their windfall profits by €354m. See Table 11 for the financial impacts of day-1 entry of generic medicines on all stakeholders. More details are provided in Annex 4, section 3.c.iii.

Table 11 – financial impacts of day-1 entry of generic medicines	Systemic change (10 medicines)
Originator gross profit	**-€354m**
Generic gross profit	+€50m
Cost to public payer	**-€200m**
Δ of patients treated (monetised)	+€160m
Patients + payer monetised gain/loss	**+€360m**

Abolishing the paediatric market exclusivity extension[169] for completing PIPs will better regulate a system that is currently not functioning very well. At present, the paediatric regulation offers 6 months of SPC extension for completing a PIP, and for orphan medicines 2 years of market exclusivity extension. However, there are several SPC protected orphan medicines with 13-14-15 years of protection duration[170]. For these products a 10+2 years market exclusivity is of less value and they would be better off with a 6 months extension of the SPC protection. To switch to this protection, they need to renounce their orphan designation and they often do so. The abolition of the paediatric extension of market exclusivity is thus expected to improve clarity in the system.

The measure will also imply that orphan medicines not protected by SPC but eligible to complete a PIP, will lose the 2-year extra market exclusivity protection available in the baseline. However, from the entry into force of the Paediatric Regulation up to 2020, only 11 of these market exclusivity extensions were granted[171], meaning that it has been a rarely used incentive. With 1 such incentive not granted per year in the future, the public would save €96m per year. The affected originator companies would lose €94m in gross profits over the medicine's lifetime each, but due to the few uses, the impact on the whole industry is not significant. More details are provided in Annex 4 section 3.c.iv.

Table 12 – Impact of abolishing 2 years ME extension for completed PIP	Systemic change (1 medicine)
Originator gross profit	**-€94m**
Generic gross profit	+€13m
Cost to public payer	**-€54m**
Δ of patients treated (monetised)	**+€42m**
Patients + payer monetised gain/loss	**+€96m**

[167] See also Section 5.2 of this SWD (common elements).
[168] This is different to the general pharma legislation, where regulatory data protection is designed in a way to allow generic filing before expiry.
[169] This measure is regulated in the Paediatric Regulation and it is mentioned as a common elements of the revision of the paediatric legislation, however it changes the market exclusivity period, therefore its impact is relevant for orphan products therefore it is discussed in this section.
[170] See also Table 3 (length of protection of orphan medicines by type of protection).
[171] EMA data.

The introduction of the global marketing exclusivity (GMA) will limit stacking market exclusivity periods for additional orphan indications and should lead to a simplification of the system. The GMA prolongs the existing market exclusivity by only 1 year in all orphan indications. The use of this incentive is maximised at two indications, i.e. maximum 2 years of prolongation of the ME will be possible. Furthermore, market exclusivity granted **to a second generation product** that is similar to the first generation product will not be applied in respect of generic products of the first reference product for which the market exclusivity expired to avoid so called evergreening[172].

The GMA would concern 16% of orphan medicines, those with multiple orphan indications. For them it would mean replacing 4.2 years of partial protection for additional indication with on average by 1.3[173] years complete protection of the medicine. Importantly, this would put a limit on 'orphan blockbusters' with several indications, and disincentives on gaming the system for artificially inflated protection periods. More details are provided in Annex 4 section 4.

Enhanced regulatory support for HUMN products will improve study designs, support developers especially SMEs and those with less regulatory knowledge, reduce assessment time and increase quality of evidence. It can ultimately allow those products come to the market earlier, provided the benefits outweigh the risks, increasing the number of new orphan medicines per year. **Companies that lose commercial interest in marketing an orphan product** will be encouraged to offer it for transfer to another company rather than withdrawing it, therefore contributing to an increased number of products staying on the market. **The capping of an orphan designation at 7-years** is expected to act as push to developers for faster translation from orphan designation to authorisation. **Abolishing the orphan designation criterion on the basis of return on investment** will reduce the regulatory burden and provide a more flexible regulatory framework. The **transfer of the responsibility for adopting decisions** on 'orphan designations' from the Commission to the Agency will provide more effective and efficient procedures.

6.1.2 Combined impact of the measures

Option A

The combined impact of the measures is shown below in Figure 4, depicting the cost-benefits of Option A on all stakeholders.

Figure 4 – cost/benefits for all stakeholders of Option A[174]

	Cost/benefit for **public payer and patients**	Cost/benefit for **originators**	Cost/benefit for **generic industry**
Option specific measures			
Keeping the baseline ME	Neutralising general pharma's access gains	0	0
Novel incentive – voucher for HUMN	+€994m additional cost +1-2 additional HUMN medicines per year	+€151m gross profit for HUMN developer +€576m gross profit for voucher buyers	- €122m gross profit

[172] See also Section 5.2 of this SWD.
[173] The weighted average of protection for medicines with one or more additional indication
[174] Public payers' costs are under 'public authority' section; originators mean marketing authorisation holders of an original version of the medicinal products, as opposed to generic industry. Interests of those SMEs, which are involved in R&D of original products, correspond to interests of originators.

Common elements			
Day-1 entry of generic/biosimilars after ME expiry	€360m cost saving	-€354m gross profit	+€50m gross profit Predictable market entry
Abolishing 2-year ME extension for completing PIP	€96m cost saving legal clarity	-€94m gross profit	+€13m gross profit
Global marketing exclusivity	cost neutral, more predictable	Shorter protection time Stronger protection =cost neutral	cost neutral, more predictable
Total balance	**+€538m extra cost** +1-2 additional HUMN medicines per year **Lower access**	**+€279m gross profit** **Unfair and inefficient distribution of profits**	**-€59m gross profit**

Conduct of business: The additional reward in the form of a transferable exclusivity voucher will increase the profits of industry (originators including SMEs), although disproportionately for the voucher *buyers* rather than for the HUMN developers in view of the potential high number of vouchers. It is therefore not expected to have positive impacts on HUMN developments. Moreover, keeping the same length of market exclusivity for all orphan medicines, which is detached from their investment costs and level of innovation addressed, may lead to overcompensation of some pharmaceutical companies. Introducing increased scientific support for HUMN would be positive for business engaged in areas of more risky research (often SMEs). All the measures aimed at the faster generic/biosimilars competition[175] are expected to have a positive effect for generic industry. As these measures are aimed to avoid unjustified benefits being drawn from the market exclusivity, the overall impact on the conduct of business would be positive.

Other common element measures aimed at improving patients' access (transfer to another company rather than withdrawing an orphan medicine; capping the duration of the orphan designation at 7 years) will be of limited effect for businesses. Still, the transfer of an orphan medicine, facilitated by publishing the intention of withdrawal, could have a positive impact on the conduct of business.

Providing for the possibility to adapt the current definition of an orphan condition to ensure that the legislation is 'fit' to embrace technological and scientific advances would have a positive impact on businesses. Removing the orphan designation criterion of return on investment will have no impact on businesses since it has never been used[176] (although it will simplify the system). Transfer of responsibility for adopting decisions on 'orphan designations' from the Commission to the Agency will create a faster decision-making and, therefore, a positive impact on conduct of business. **SMEs:** as SMEs are involved mostly in early stage of R&D and invest in riskier areas of R&D targeting innovative products, transferrable exclusivity vouchers could potentially increase the value of their research assets/authorised product once sold to big pharma, however due to the high number of vouchers, such a positive impact would be diluted.

[175] Generics/biosimilars can enter the market at day-1 of the expiry of the exclusivity period; Reduction of consecutive periods of market exclusivity for new indications of the same orphan medicine by introducing them under the same "Global Marketing Authorisation" (GMA); the market exclusivity granted to a second generation product that is similar to the first generation product shall not be applied in respect of generic products of the first reference product for which the market exclusivity expired.
[176] Section 5.1 of the Joint Evaluation.

Public authorities: The introduction of a voucher may carry a significant cost to the national authorities as longer exclusivity periods will delay entry of cheaper generics.

Impacts on R&D / innovation: The additional incentives will support increased return on investment for developers and bring additional investment into R&D for HUMN. However, in the case of vouchers a more limited impact is expected as due to the potential high number of vouchers, their value will diminish.

Administrative burden: Procedural simplifications will reduce administrative burden.

Internal market: The impact on the internal market can mainly be seen from the viewpoint of the number of new products on the market, their availability and patient's access across the EU. The new incentives would increase the number and availability of new orphan medicines. On the other hand, lack of specific measures to achieve EU-wide market launch and patient access would retain the level of fragmentation of the internal market as in the baseline. Delayed generic entry would hinder competition, and keep prices high for a longer period compared to the baseline.

Competitiveness/trade: The special incentives for HUMN, including the transferable voucher, and common measures for simplification are expected to improve competitiveness and attractiveness of the EU pharmaceutical sector, especially SMEs, and support increased investment in medicine development to address unmet medical needs.

Digital impact: Measures that are being considered in the revision of the general pharmaceutical legislation (for example the digitalisation of procedures and the possibility to analyse real world data) are expected to support pharmaceutical companies and public authorities to enjoy the benefits coming from digital innovation in the sector. The European Health Data Space[177] will provide a common framework across Member States for the access to high-quality real world health data and will be particularly relevant for small patient populations. The data, for example collected through rare disease registries, will become accessible and are expected to allow progress in research and development of medicines and provide new tools in pharmacovigilance.

Option B

The combined impact of the measures is shown below in Figure 5, depicting the cost-benefits of Option B on all stakeholders.

Figure 5 – cost/benefits for all stakeholders of Option B

	Cost/benefit for **public payer and patients**	Cost/benefit for **originators**	Cost/benefit for **generic industry**
Option specific measures			
No market exclusivity	+€725m cost savings Political signal to divest rare disease R&D likely 1-2 HUMN less per year	-€751m gross profit	+€101m gross profit
Common elements			
Day-1 entry of generic/biosimilars after ME expiry	€360m cost saving	-€354m gross profit	+€50m gross profit Predictable market entry

[177] COM(2022) 197 final.

Abolishing 2-year ME extension for completing PIP	€96m cost saving legal clarity	-€94m gross profit	+€13m gross profit
Global marketing exclusivity	cost neutral, more predictable	Shorter protection time Stronger protection =cost neutral	cost neutral, more predictable
Total balance	**€1.181m cost saving** **1-2 HUMN less medicines per year** **0% increase in access**	**-€1.199m gross profit**	**+€164m gross profit**

Conduct of business: Absence of market exclusivity is expected to result in less R&D in medicines for rare diseases, as originators will not have an incentive to engage in such R&D. Generic entries will gain faster access to the market, however, there will be also a smaller number of new original products, which could offset to some extent this gain. The impact of common elements in this option is similar as for Option A. **SMEs:** No market exclusivity will particularly negatively impact SMEs involved in R&D as they will face a high risk that no big company will be eager to buy the result of their R&D if this incentive is abolished. In consequence, they may find it too economically risky to engage in R&D of orphan products.

Public authorities: Health payers may benefit from lower average costs for medicines due to earlier generic entry. The extent of these benefits will depend on originators' response to the absence of the reward, and it is possible that average prices will be adjusted upwards to some degree to offset the elimination of the compensation mechanism. However, these savings for public authorities should also be seen in the perspective of costs related to the lack of adequate treatments (see also the following subchapter under 'social impacts of the policy options').

Impacts on R&D / innovation: The absence of a reward in the form of market exclusivity may lead to the reprioritisation of research in the area of orphan products and, hence, negatively affect investment into R&D neutralising the positive effects of the common elements for the development of new products in particular in areas of HUMN.

Administrative burden: Simplification of procedures (common elements) is expected to bring positive results.

Digital impact: The digital impact in this option is similar as for Option A.

Internal market: Earlier generic entry due to the elimination of the reward may in theory improve access, but any gains for the internal market may be offset by the absence or belated availability of new orphan products aimed at areas of HUMN and innovative orphan products.

Competitiveness/trade: Elimination of the market exclusivity could weaken the global competiveness of EU based originators compared with the current situation, which is not expected to be outbalanced by positive aspects of procedural simplifications from the common elements.

Option C

The combined impact of the measures is shown below in Figure 6, depicting the cost-benefits of Option C on all stakeholders.

Figure 6 – cost/benefits for all stakeholders of Option C

	Cost/benefit for **public payer and patients**	Cost/benefit for **originators**	Cost/benefit for **generic industry**
Option specific measures			
+1 year of ME for HUMN addressing medicines	+€82m additional cost 1-2 additional HUMN medicines per year	+€94m gross profit	- €13m gross profit
1 year of ME conditional for full EU launch	€288m cost saving from non-complying medicines (6 non-complying MP) Broader and faster access to complying medicines	-€282m gross profit loss (6 non-complying MP) +€4m additional cost (4 complying MP)	+€38m gross profit gain due to non-complying medicines (6 non-complying MP)
Common elements			
Day-1 entry of generic/biosimilars after ME expiry	€360m cost saving	-€354m gross profit loss	+€50m gross profit Predictable market entry
Abolishing 2-year ME extension for completing PIP	€96m cost saving legal clarity	-€94m gross profit loss	+€13m gross profit
Global marketing exclusivity	cost neutral, more predictable	Shorter protection time Stronger protection =cost neutral	cost neutral, more predictable
Total balance	**€662m cost saving** **+1-2 additional HUMN** **+9% broader and faster access**	**-€640m gross profit loss**	**+€88m gross profit**

Conduct of business: The modulation of market exclusivity duration is expected to target those areas where research is mostly needed and where the investments are most risky, therefore would contribute to a fairer distribution of incentives. The impact of common elements in this option is similar to Option A.

SMEs: The 10-year market exclusivity for products addressing HUMN and innovative products will benefit SMEs (active in riskier R&D). Although the 10-year market exclusivity period corresponds to the current baseline, by the fact that market exclusivity periods will be differentiated, the relative value of HUMN/innovative products will increase. As to the common elements, their costs are expected to be the same across all the options (for details see Option A).

Public authorities: The costs to national health systems are expected to increase, as compared to the baseline, due to an increase of the maximum market exclusivity periods (10 years + 1 year for the market launch in the whole EU + max. 2 years for new indications) and thus delayed entry of generics. The reduced (compared to the baseline) 5-year market exclusivity period, as applicable to products with well-established use, is not expected to result in major significant reduction of costs to public authorities costs.

Impacts on R&D / innovation: Additional ME, given for orphan products which address HUMN and innovative products will boost R&D in those areas.

Administrative burden: The impact of administrative costs is similar as for Option A, i.e. less administrative burden is expected, thanks to procedural simplifications. Some additional documentation may be required for eligibility for the HUMN category, and hence for additional ME.

Digital impact: The digital impact in this option is similar as for Option A.

Internal market: The effect on the internal market (availability and patient access) is expected to be positive due to an additional ME period for EU-wide launch as well as access-inducing measures from the common elements.

Competitiveness/trade: The system of modulated ME is expected to boost competitiveness and attractiveness of the EU pharmaceutical sector and support increased investment in orphan medicines development. The common elements such as procedural simplification are expected to have a further positive effect.

6.1.3 Social impacts of the policy options

The revision of the orphan regulation aims to meet two *societal* needs:

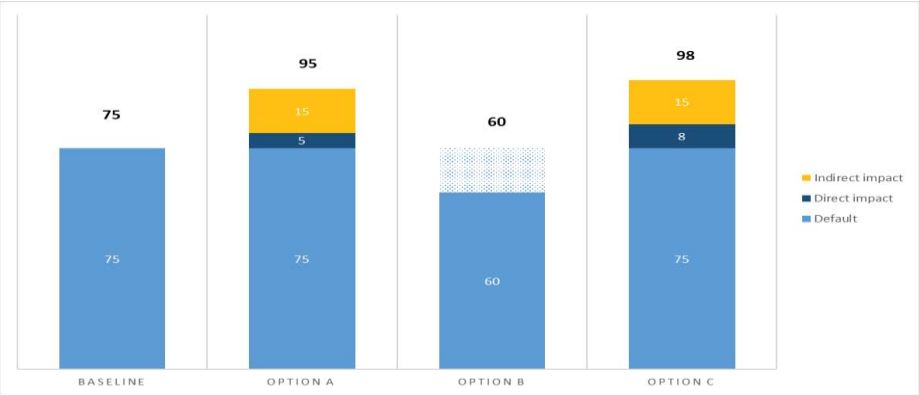
- Increase therapeutic options for rare disease patients, especially in disease areas where therapies do not exist or are insufficiently effective (high unmet medical needs - HUMN).
- Ensure better and equal patient access to medicines for rare disease across the EU.

Therefore, we measure the social impacts by two indicators: 1. Number of medicines addressing HUMN and 2. The increase in patient access.

Medicines addressing HUMN

Orphan medicines addressing HUMN can be considered more valuable to society than other new medicines, because of the lack of any existing alternative and the existing burden for patients and health systems. This does not undermine the value of development of medicines for other rare diseases as the existence of more than one therapeutic options benefit patients, health care professionals and increase competition. Figure 7 below summarises the expected change in number of medicines addressing HUMN under the different options[178].

Figure 7 - Expected number of HUMN addressing orphans in the various policy options.



Option A maintains the baseline incentives and adds the vouchers on top of it for HUMN products. It could stimulate extra investment in HUMN products. The downside of the vouchers is that it may

[178] Apart from the social impact of Options A/B/C, there is also the common element to all options of the **adaptation of the current definition of an orphan condition** to ensure that the legislation is better 'fit' to embrace technological and scientific advances. This will support the development of products in HUMN areas (and should also cater for more efficient procedures for designation and authorisation).

become a very expensive and inefficient way of rewarding developers. We estimate that compared to the baseline (75 HUMN for 15 years), the **overall number of HUMN products could go up to 80** with the additional incentive (direct impact).

Option B is not only indifferent to HUMN medicines, but it abolishes the market exclusivity, sending a negative signal to orphan medicine developers targeting the European market, namely that orphan medicines are not anymore a priority in the pharmaceutical legislation. This signal would likely trickle down to research funders, investors and national authorities, resulting in a decline in orphan medicines, and consequently a decline in HUMN medicines too. **An estimated 20% decline in newly authorised orphan medicines** would bring down the number of **HUMN addressing orphans to 60** in the next 15 years.

Option C offers a modulation of market exclusivity period, favouring medicines addressing HUMN and rewarding them with 1-year additional protection. This translates into a 14% higher protected revenue, or 7.7% higher gross-profits compared to other medicines, making their development and authorisation more rewarding commercially. Overall, the incentive could directly **increase the number of HUMN addressing medicines by 10%, to 83** in the next 15 years (*direct* impact).

We can expect that both **Option A** and **C** will also have important *indirect* impacts. An EU level definition of HUMN under the common elements could lead to important spill-over effects, just as it happened with the introduction of the orphan designation in the EU Orphan Regulation in 2000[179].

All these spill-over effects led to a successful market creation that boosts investment and innovation. A definition of HUMN would therefore allow labelling research and medicinal products that have highest utility for society, and channel public resources – either research funding or favourable P&R conditions – towards them. The extra benefit given for HUMN in the orphan regulation would showcase the EU's commitment, and invite other actors to follow suit in their own realms.

Improving access to orphan medicines

The revision of the *general* pharma legislation proposes a solution where 1 year of additional regulatory protection would be granted in case the medicine is launched in all EU countries within 2 years from authorisation. According to the analysis conducted in the impact assessment of the general pharmaceutical legislation[180], this not only would increase the number of Member States with access (and thus the percentage of the EU population covered), but the medicine would also be made available for more people in a significantly shorter time than in the baseline.

Option A by keeping the market exclusivity at 10 years without any modulation, would nullify the access conditionality introduced in the general pharma legislation. Option A would therefore equal the current status quo (baseline).

Option B, which abolishes market exclusivity, would leave the protection period defined only by the general pharma for orphan medicines. The general pharma legislation will incentivise access, and it is worthwhile for companies to make an effort to launch in all Member States. Option B should result in higher and faster access than the baseline.

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[179] At the time, an important win for orphan developers was not the market exclusivity alone, but also the recognition of rare diseases by many different actors. National and international research funders, notably EU's Horizon and its predecessor framework programmes, started providing dedicated funding for rare disease research after this recognition. Furthermore, national HTA and pricing & reimbursement authorities recognised that orphan medicines deserve more flexible and tailored rules, creating favourable market conditions for them. And European Reference Networks (ERNs) were established to improve rare disease patients' access to expertise, diagnosis and treatment across the EU. See also Section 1.3 of this SWD.

[180] Staff Working Document – Impact assessment on the general pharmaceutical legislation (Annex 4)

Option C modulates the market exclusivity mirroring the general pharma. Thus, it would preserve the incentive for improving access, just from a higher basis (9 year default market exclusivity vs. 8 year default regulatory protection). We expect therefore a similar impact for option B and C.

Figure 8 – Percentage of population served over time

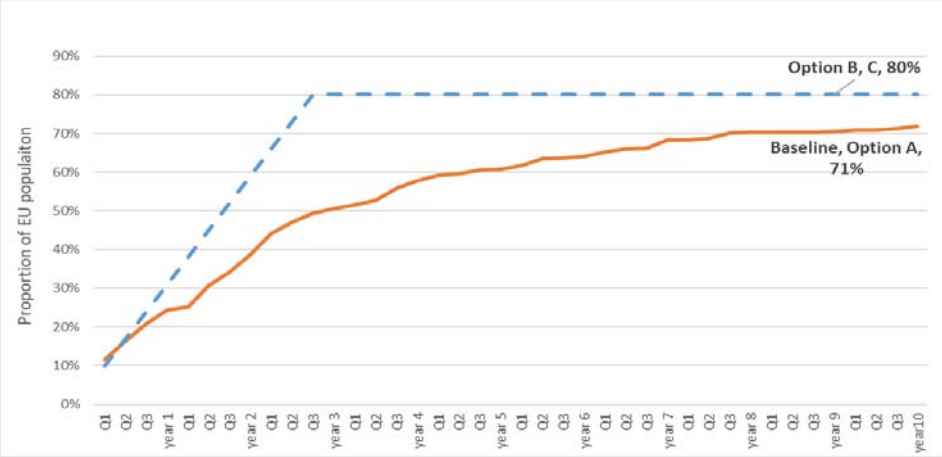


Figure 8 demonstrates the expected impacts of the various policy options on patient access[181]. Option B and C reach a higher plateau of 80% EU population covered, and also much faster than Option A/baseline, two years following authorisation.

Stakeholder views on HUMN and access

All stakeholder groups were in favour of better focus on HUMN. However, **pharmaceutical industry** is not in favour of strict HUMN criteria whereas **health payers/public authorities** support this idea. **Pharmaceutical industry** is strongly against linking the provision of the market exclusivity with launching obligations, whereas health payers/public authorities were mixed in their views. Other common elements (enhanced regulatory support for HUMN products, addressing regulatory limitations, possibility to transfer a marketing authorisation to another company rather than withdrawing, capping of an orphan designation at 7-years) were overall supported by all stakeholder groups.

6.2 Medicines for children

6.2.1 Economic impacts of the policy options

The economic impacts of the policy options on the main stakeholders (industry, public authorities, patients) has been assessed and quantified by focusing on: a) assessing the potential effects of changes to the extension of the SPC under the various options (including the introduction of a novel reward under option A); b) assessing the impact of the common elements. Other economic impacts have been considered and they are detailed here below by stakeholder group.

Public authorities derive benefits in the form of savings from avoided hospitalisation and avoided outpatient treatments due to the reduced number of products tested and authorised for use in children Such benefits were calculated in the Joint Evaluation on the basis of paediatric products developed and resulted in minor, almost irrelevant impacts therefore these benefits have not been considered in the current economic analysis (more details are provided in the social impact section). Concerning the costs, they are impacted by the costs of medicinal products linked also to the length of

[181] It is hereby important to keep in mind that these incentives work with medicines that are not protected by SPC or patents, as those IP incentives provide longer protection than the maximum achievable market exclusivity for more than half of all newly authorised medicines.

protections which delays the entry of generic medicines. The proposed options are not expected to produce administrative costs for public authorities.

The **innovative pharmaceutical industry** incurs two types of costs: clinical research costs linked to the obligation to study any new medicines for use in children and administrative costs linked to the PIP procedure. The options proposed are not expected to impact the costs of conducting paediatric studies but are instead expected to have an impact on the administrative costs linked to PIPs. Industry benefits derive from the rewards provided for the completion of the paediatric studies and the sale of the products. The **generic industry** is not concerned by the PIP obligations and they have no obligation to include paediatric indications or formulations developed by the originators. The SPC extension delays generic competition by 6 months, but this is not necessarily revenue lost, rather delayed. The generic industry is concerned more by the non-predictability of the SPC system (which is regulated by a separate piece of legislation[182] currently under revision and where a unitary SPC system has been explored) due to the different handling by each national patent office than by the SPC extension in itself. The impact of the elimination of the extension of two extra years of marketing exclusivity for paediatric orphan medicines with completed PIP is analysed in Section 6.1.1.

Patients' costs and benefits derive from delayed/faster access to the products developed. Other impact on patients are assessed in the social impact section.

Which medicines are affected by changes in SPC extension?

The paediatric regulation's key feature is the obligation for medicine developers to carry out PIPs and the reward that it offers in form of SPC extension to compensate the companies' efforts[183]. The policy options in the current revision offer different duration of the SPC extension. Analysing our basket of medicines from the IQVIA database[184] reveals that 20% of newly authorised medicines have claimed and used the incentive in the recent past[185]. We, therefore assume that 10 medicines per year will receive the extension 15 years from now.

Table 13 - Comparison of medicines with paediatric extension to medicines without extension

	Number of products	Avg. protection period	Avg. peak annual revenues
Medicines with paediatric extension	40 (20%)	14.3 years	€ 540.6 m
All other medicines	159 (80%)	12.7 years	€ 199.5 m

Table 13 also demonstrates, that the medicines benefitting from the SPC paediatric reward generate far higher revenues than those that do not benefit from this. More details in Annex 4 section 7.

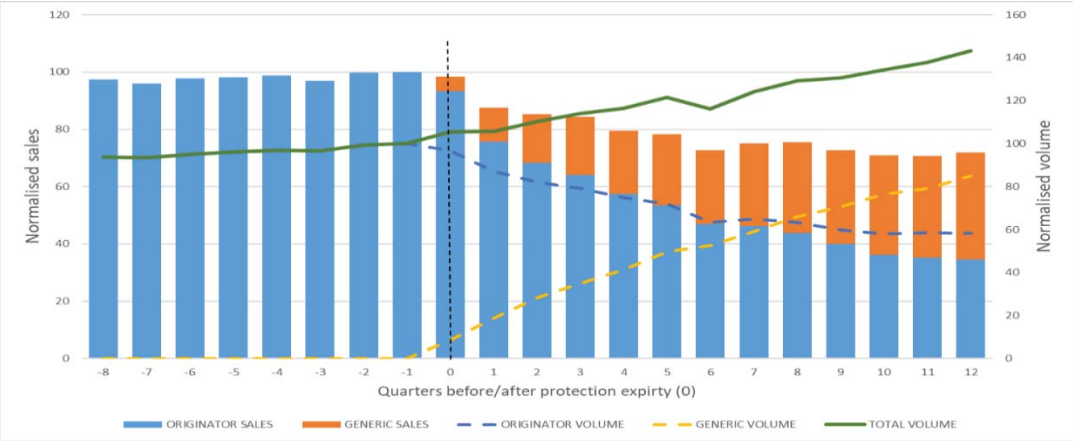
How the SPC extension generates value/cost for stakeholders

In analysing the impacts of changes in the SPC extension, we use the same model as for the general pharma and orphan medicines. The model represents an innovative medicine, an analogue, for which the paediatric SPC extension is the last layer of protection from generic competition. To create this

[182] Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the supplementary protection certificate for medicinal product.
[183] Section 5.2.4 of the Joint Evaluation finds that the average cost to complete a PIP is around €20 million.
[184] The same cohort of medicines that was used in the general pharma and for orphan medicines, a basket of 199 medicines with protection expiry between 2016 and 2024.
[185] The IQVIA database does not specify which medicines were subject to the PIP obligation of were granted a deferral. It should also be considered that for some products the PIP was not yet completed at the moment of the MA and therefore the SPC extension could not yet be claimed. Delays in receiving the SPC extension from national patent offices cannot be ruled out.

analogue, historical data[186] were used. More details in Annex 4 section 7.b. The sales of the originator products and their generic/biosimilar competitors from 2 years before to 3 years after protection expiry were analysed in Figure 9 below.

Figure 9 - Modelling generic entry after SPC extension expiry



The model uses normalised units to represent prices and volumes across different products, where 100 is equal to originator's peak sales, at quarter -1 (the last quarter before generic/biosimilar competition)

As shown in Table 13 below, medicines benefiting from SPC paediatric extension are generally characterised by high sales, they are prime targets for generic/biosimilar competition. Here we see more competitors coming after protection expiry, a more aggressive substitution of originators by generics/biosimilars and a steeper price erosion (and public cost saving) after expiry. The stakes are also higher both for companies and public payers, one year monopoly means a lot of profit/lot of public cost. More details in Annex 4 section 7.e).

Option A – 6 months SPC extension + novel incentives

Option A proposes extra incentives if a PIP is completed for a product that addresses an unmet medical need (UMN). We expect that 20% of the new products will meet the UMN criteria[187], therefore out of the expected yearly 10 SPC extension, 2 would be for UMN addressing medicine. One measure considered is to give +12 months SPC extension for these products, instead of the current +6 months. The economic impacts of such a measure on the different stakeholders, estimated using the model set out above, are presented both for a single product, and at systemic level (for the 2 benefiting products) in Table 14. Annex 4 section 7.c presents the detailed calculations.

Table 14 - impact of 6 months protection increase (+12 months SPC extension) for UMN on different stakeholders

	avg product (€540 m annual sales)	Systemic impact (2 extensions/year)
Originator gross profit	**+€169 m**	**+€338 m**
Generic gross profit	-€32 m	-€64 m
Public payer's gain/loss (cash)	-€78 m	-€156 m
Δ of patients treated (monetised)	-€78 m	-€156 m
Patient and payer gain/loss	**-€156 m**	**-€312 m**

[186] A basket of 11 products with paediatric SPC extension expiry between 2016 and 2018 served the basis of the analogue

[187] Based on historical data of how many products authorised for use in children would qualify as UMN products.

Thus, benefiting originator companies would increase profits by €338 m at a cost of €312 m to the public.

The analysis of the impact of the introduction of a regulatory protection voucher for medicines addressing UMN is provided in section 6.3 (orphan option A). It concludes that if there are high numbers of vouchers distributed, it becomes a costly and ineffective instrument and this is *a fortiori* applicable for paediatric medicines[188]. More details in Annex 4 section 5).

Stakeholder views: the possibility of increasing the protection of products completing PIPs is supported at least partially by industry and some researchers. For example industry would favour an increase in the rewards if an obligation to conduct PIP on the basis of the mechanism of action of their product would be introduced. Some researchers and patients organisation would favour an increased reward for development in some specific areas, for example rare paediatric cancers. Competent authorities oppose to any additional rewards in particular under the form of vouchers.

Option B – no SPC extension

Under option B, medicines which would currently be eligible for the 6-months SPC extension will lose such protection. Generic medicines could enter the market earlier and public authorities would pay less, for more patients served. We have adjusted our model to the new expiry and compared it to the baseline. Table 15 shows the impact of the change for all stakeholders, both at an individual product level, and at systemic level for all 10 products, that would benefit from the extension in the baseline.

Table 15 - impact of 6 months protection reduction on different stakeholders

	avg product (€540 m annual sales)	Systemic impact (10 extensions/year)
Originator gross profit	**-€169 m**	**-€1,690 m**
Generic gross profit	+€33 m	+€330 m
Public payer's gain/loss	+€76 m	+€760 m
Δ of patients treated (monetised)	+€75 m	+€750 m
Patient and payer gain/loss	**+€151 m**	**+€1,510 m**

At an individual product level, the reduction is a significant loss to the **originator company**, an average SPC extended product would lose -€169 m gross profit. The **generic** products would have +€33 m higher profits thanks to the earlier entry. The **public payer** would experience +€76 m yearly savings, however this is not the only benefit for the public. Not only the total cost would be less, but more **patients** could be served with the more affordable medicine, adding an additional +€75 m monetised patient benefit. Overall the public gains €151 m thanks to the reduction. Looking at systemic level, the loss of 10 SPC extensions compared to the baseline would cause €1.690 m profit loss to the innovator industry annually. On the other hand, the public would make significant savings, to the tune of €1,510 m per year. More details in Annex 7 section 7.d.

Stakeholder views: During the stakeholder consultation none of the stakeholder groups supported the abolishment of the SPC extension. There is a broad consensus that the paediatric regulation works overall well, delivers the needed studies for children, and the incentive is perceived as a significant element of the good performance.

Option C – 6 months SPC extension

[188] Looking at historical data 30% of products authorised with paediatric indications could be classified as fulfilling the UMN criteria.

Option C preserves the baseline SPC extension reward, therefore compared to the baseline this measure has a neutral economic impact. Despite not changing the SPC extension, together with the common elements option C could tackle the objectives of the revision.

Impacts of common elements

Support for products addressing UMN – The possibility to benefit from dedicated research funding and later by early support by the Agency for products considered as having the potential to address UMN of children, is expected to increase the number of these products authorised for use in children. The measure is also expected to increase predictability of the outcome of their development for companies and be advantageous in particular for SME who may be facilitated in raising capitals from investors for these products.

Evolutionary PIP - This streamlined process could affect up to 25-30 % of the procedures. There would be an increased effort for EMA's Paediatric Committee (+ 10-20 %), but a reduced burden for industry (30%) due also to a better alignment with the US system. This measure is expected to positively influence SMEs, as they are more likely to benefit from lower administrative burdens respective to their scale and ability to bear sunk costs as part of their business model.

Simplified PIP - A less demanding PIP could be granted in selected situations such is the case of the paediatric only products to reduce burden and timing of the PIP preparation and application. A simplified PIP may also be used for PUMA products. It is difficult to predict the impact of the measure as it cannot be anticipated the number of paediatric only products which will be submitted. However, it is expected to have a similar impact on SMEs as the Evolutionary PIP.

The change in the waiver system to take into account the **mechanism of action** of a product has been estimated that it would lead to 8.3% more PIPs, including the UMN ones. This would translate into 3 additional PIPs per year, and 1 additional SPC extension reward. This measure is also expected to encourage the use of digitalised methods of genetic screening of the causes of diseases by the industry and academics, affecting SMEs more than larger pharmaceutical companies. The measure would require also SMEs to study a product on diseases where they do not have the necessary knowledge/expertise available in house and consequently increase their costs.

Cap in the maximum length of the duration of the deferrals which can be granted to completion of a PIP. This element is expected to reduce the average duration of 18% of PIPs.

6.2.2 Combined impact of the measures

Option A

	Cost/benefit for **public payer and patients**	Cost/benefit for **originators**	Cost/benefit for **generic industry**
Option specific measures			
Additional 6 months SPC extension for UMN	+€156m cost	+€338m gross profit	-€64m gross profit
Common elements			
Mechanism of action	3 more PIPs +€151m cost resulting from additiona1 SPC extension	+€169m gross profit +€66m cost	-€33m gross profit
Cap in the maximum length of the deferrals	Faster completion of PIPs Cost neutral	Cost neutral	Cost neutral
Total balance	**+€307m cost** **+3 PIP** **+earlier access**	**+€441m gross profit**	**-€97m gross profit**

Conduct of business: The higher reward compared to today for the completion of PIPs would have a positive effect on businesses that invest in products addressing UMN. However, the introduction of

a voucher system is not considered to have positive impacts on developers of the UMN products due to the potential high number of vouchers; it may even undermine the use of such a scheme in the area of antimicrobials. Moreover, this option could negatively impact the generic and biosimilar industry as it would further delay their access to the market. No specific effect from this option is expected for SMEs. Originators will incur into extra costs for conducting on average 3 extra PIP/year due to the introduction of the mechanism of action provision[189].

Public authorities: The introduction of an additional reward providing longer protection periods may carry a significant costs to national health systems and payers by delaying generic entry.

Impacts on R&D / innovation: The additional incentives will support increased return on investment for developers and bring additional investment into R&D for UMN. However, in the case of vouchers a more limited impact is expected as due to the potential high number of vouchers, their value may be low.

Administrative burden: Reduction is expected to derive from the common elements. In particular:

- *Evolutionary PIP:* This streamlined process could affect up to 25-30 % of the procedures. There would be an increased effort for EMA's Paediatric Committee (+ 10-20 %), but a reduced burden for industry (30%) due also to a better alignment with the US system.
- *Simplified PIP:* A less demanding PIP could be granted in selected situations, such is the case of the paediatric only products, to reduce burden and timing of the PIP preparation and application. A simplified PIP may also be implemented in case of PUMA products. It is difficult to predict the impact of the measure as it cannot be anticipated the number of paediatric only products which will be submitted.

Digital-by-default / digital ready policy making: The introduction as a common element of the obligation to take into account the molecular mechanism of action of a product when designing a PIP are expected to encourage the use of digitalised methods of genetic screening of the causes of diseases by the industry and academics

Internal market: While the increases in the number of new medicines for children owing to the new incentives provided improve the functioning of the internal market, delayed generic entry would hinder competition, and keep prices high for a longer period compared to the baseline.

Competitiveness/trade: The special incentives for UMN, including the transferable voucher and EU-wide market launch are expected to improve competitiveness and attractiveness of the EU pharmaceutical sector and support increased investment in medicine development to address UMN. The common elements evolutionary PIP and the consideration of the mechanism of action of a product in the design of a PIP would bring the European system close to the system in place for medicines for children in the US, therefore increasing the competitiveness of the EU pharmaceutical sector as companies tend to operate globally

Option B

	Cost/benefit for **public payer and patients**	Cost/benefit for **originators**	Cost/benefit for **generic industry**
Option specific measures			
Maintaining current extension	€1.510m cost saving	-€1.690 m gross profit	+€330m gross profit
Common elements			

[189] The costs of the conduction of a PIP has been estimated in around 22m euro. Joint evaluation of the orphan and paediatric regulation.

Mechanism of action	3 more PIPs	+€66m cost	0
Cap in the maximum length of the deferrals	Faster completion of PIPs Cost neutral	Cost neutral	Cost neutral
Total balance	**+€1.510m cost saving** **+3 PIP** **+earlier access**	**-€1.756m gross profit** **No compensation for carrying out PIPs**	**+€330m gross profit**

Conduct of business: The elimination of the reward for the completion of the PIP will mean that companies have to cover the costs for the paediatric development themselves and can no longer count on the reward as a compensation for clinical studies stemming from the paediatric legislation. Generic and biosimilar industry may benefit from slightly earlier market entry by 6 months. However, the generic biosimilar version may not necessarily include the paediatric formulations (generics have no obligation to develop and market paediatric adapted formulations of their products) hence not serving children. The deletion of the SPC extension would negatively affect in particular SMEs as they may find it more difficult to raise funding due to the possible non/low profitability of their products.

Public authorities: Health payers may benefit from lower average costs for medicines due to earlier generic entry. The extent of these benefits will depend on originators' response to the absence of the reward, and it is possible that average prices will be adjusted upwards to some degree to offset the elimination of the compensation mechanism.

Impacts on R&D / innovation: The absence of a reward for public research may negatively impact the quality and lead to the deprioritisation of paediatric research for some products and hence negatively affect investment into R&D neutralising the positive effects of the common elements for the development of new products in particular in areas of UMN for children

Administrative burden and digital by default: similar as for option A.

Internal market: Earlier generic entry due to the elimination of the reward may in theory improve access, but this does not concern paediatric versions of those medicines as generics have no obligation to develop and market paediatric formulations. Hence, any gains for the internal market would be offset by the absence or belated availability of paediatric versions of adult products.

Competitiveness/trade: Elimination of the SPC reward could weaken the global competiveness of EU based originators compared with the current situation. It may moreover decrease attractiveness, as the obligation would be maintained without any reward.

Option C

	Cost/benefit for **public payer and patients**	Cost/benefit for **originators**	Cost/benefit for **generic industry**
Option specific measures			
Maintaining current extension	Cost neutral	Cost neutral	Cost neutral
Common elements			
Mechanism of action	3 more PIPs +€151m cost (1 SPC extension)	+€169m gross profit +€66m cost	-€33m gross profit
Cap in the maximum length of the deferrals	Faster completion of PIPs Cost neutral	Cost neutral	Cost neutral
Total balance	**+€151m cost** **+3 PIP** **+earlier access**	**+€103m gross profit**	**-€33m gross profit**

Conduct of business: Under this option, companies will obtain the same reward as in the baseline. The common elements will support companies to develop products in particular in areas of UMN.

Early support mechanism is expected to be beneficial in particular to SMEs. Compared to the baseline, generic and biosimilar industry would not be affected.

Public authorities: The costs to national health derives from the additional products that are expected to be developed due to the introduction of the common elements (mechanism of action in particular).

Impacts on R&D / innovation: R&D investment in paediatric medicines should at least reach the baseline level, but the common elements may add additional flexibility in conducting such research, facilitating its successful completion and increase output by in terms of innovative products.

Administrative burden and digital by default: similar as for option A.

Internal market: The effect on the internal market in not expected to change compared to the baseline, both for originators and generic companies.

Competitiveness/trade: Maintaining the reward are expected to keep the competitiveness and attractiveness of the EU pharmaceutical sector and support increased investment in paediatric medicine development. The common elements evolutionary PIP and the consideration of the mechanism of action of a product in the design of a PIP would bring the European system close to the system in place for medicines for children in the US, therefore increasing the competitiveness of the EU pharmaceutical sector as companies tend to operate globally.

6.2.3 Social impacts

In terms of social impacts the objectives of the revision are clear: they desire more medicines available for use in children and as quickly as possible. Therefore, we measure the impacts by two key indicators, number of completed PIPs (and of them in UMN) and the speed of completing them.

Number of completed PIPs (including for UMN)

Option A would offer a higher protection for UMN addressing medicines on the top of the potential rewards from general pharma and orphan regulation (if orphan medicine). However it is questioned whether this incentive would indeed foster new PIPs, or only reward PIPs in UMN, that in any case would have been carried out. If the latter, option A offers limited benefit in terms of new PIPs. **Option B** would scrap the SPC paediatric extension. The elimination of the rewards for the completion of the paediatric clinical studies is expected to neutralise the positive effects of certain common elements (for example the early support by the agency for UMN products, dedicated R&D funding for these products). It is also expected to induce companies to downscale their paediatric research programs and departments. Developers would not be encouraged to initiate the development products specific for children due to the lack of specific rewards compensating the higher costs of engaging in clinical development in children. **Option C** would keep the benefits of the baseline scenario. However some common elements and in particular introducing PIPs based on the mechanism of action would lead to 8.3% more PIP. Due to the fields that are more prone to mechanism of action PIPs (oncology, neurology, immunology), we expect that a high share of these new PIPs would be for UMN.

Timely completion PIPs and timely access for patients

Option A is not considered to differ from the baseline from what concerns the timely completion of PIPs. **Option B** may delay the developments of medicines for children as companies would not be encouraged to complete quickly a PIP in order to be able to benefit from a reward. For this reason the also authorisation of medicinal products for children is expected to decrease compared to the baseline. PIPs may be completed with a longer delay compared to today. **Option C** together with the common element that caps the maximum lengths of the deferrals it is expected to speed up by several years the completion of PIPs. Other common elements simplifying and streamlining the procedures would also translate into faster development.

6.3 Impact common to orphan and paediatric medicines

6.3.1 Environmental impacts

They mainly result from their manufacturing, use and disposal, therefore is dependent from the number of products manufactured and placed on the market No specific impact derives from the measures proposed in revision of the legislation on medicines for rare diseases and for children. For this reason, no climate consistency check was conducted for this impact assessment. Measures to reduce the environmental footprint of the pharmaceutical product lifecycle are included in the revision of the *general* pharmaceutical legislation (**specific objective 4**).

These measures cover the strengthening of the environmental risk assessment as well as promoting prudent use of medicines (antimicrobials, supporting sustainable consumption, manufacturing for instance). The environmental objectives will be monitored focusing on the presence of medicines residues in the environment and on greenhouse gas emissions of EU based pharmaceutical manufacturers.

6.3.2 Impact on fundamental rights

Options A and C of both orphan and paediatric legislations, compared to the baseline are expected to have a positive impact on the **fundamental right** of patients to benefit from medical treatments under the conditions established by national laws. Those options are also consistent with the aims of the Charter of Fundamental Rights of the EU, in particular article 24 (right of children) and article 35 (health care).

7 HOW DO THE OPTIONS COMPARE?

The comparison of the policy options in relation to the baseline scenario was performed in terms of the options' overall effectiveness, efficiency, coherence, EU-added value and proportionality and taking into consideration stakeholder views.

7.1 Orphan medicinal products

7.1.1 Effectiveness

Table 16 - Overall comparison of the policy options for orphan products in terms of effectiveness

Effectiveness: contributing to achieving the policy objectives	**Baseline**	**Option A**	**Option B**	**Option C**
Objective 1: Foster innovation and R&D	0	+	-	++
- in particular for highest unmet medical needs	0	++	-	++
Objective 2: Affordability	0	--	++	+
Objective 3: Patient access	0	+/-	+	++
Objective 4[190]: Embrace scientific advances & efficient procedures	0	++	++	++
Overall social impacts	0	+	--	++
Number of HUMN products	0	+	--	++
Increase of patient access	0	--	+	++

Estimated impact compared to the baseline: + + positive, + moderately positive, –/+ neutral, – moderately negative, – – negative and – – strongly negative

[190] Objective 4 is mostly addressed by common elements to all options.

In terms of **the effectiveness** in achieving the four policy objectives, **Option C** is the most effective, as presented in Table 16 above.

On objective 1, Option C is to be the most effective in stimulating **research and innovation** of orphan medicines due to its more effective incentive to stimulate developments especially in areas of HUMN. **Option A** offers a novel incentive which likewise also focuses on the development of HUMN orphan medicines. **Option B**, which eliminates market exclusivity, would lead to fewer orphan medicines, thus being less effective. The **introduction of HUMN criteria**[191] and **enhanced regulatory support** by the Agency, under the common elements to all options will further support the overall development of products in HUMN areas.

Social impacts have been measured in relation to **objectives 1 and 3**. In this regard, the analysis mainly focused on the impact of a disease on a patient's life and health considering two main indicators: **increase in the number of HUMN products authorised** and improvement of **patient access**. **Option A** is expected to result in a fairly high total number of products addressing orphan diseases including for HUMN but will not improve patient access (as there is no conditionality between the provision of the incentives and patient access). **Option B** should lead to fewer orphan products including for HUMN and will not directly contribute to patient access. On the contrary, **Option C** should lead to more HUMN products and also to better patient access (due to the access conditionality for the extension of the market exclusivity).

As regards **objective 2**, **Option B** is the most effective as it should foster more and faster generic competition. In turn, this would benefit to the sustainability of health systems/patients as cheaper competitor products would come earlier on the market. **Option A** would be the least effective, as it keeps the current 10 years of market exclusivity and adds an extra incentive (transferable regulatory data protection voucher) thereby increasing the costs to health systems/patients and delaying possible generic competition. **Option C**, on the contrary, would incentivise products in areas of HUMN and promote earlier market entry for other categories of orphan medicinal products. The introduction of a Global Marketing Authorisation and measures to foster faster generic/biosimilar entry of competitor products, all under the **common elements to all options**, are also going to support affordability for payers/health systems.

Regarding **objective 3**, **Option C** is the most effective to ensure **timely access** in more Member States thanks to the combination of a variable market exclusivity scheme for different product categories and incentives for companies to make orphan medicines accessible in all Member States. **Option A** falls short in comparison as transferrable voucher schemes lead to delayed entry of generics, high financial burden of Member States and thus will not improve the existing uneven access to (orphan) medicinal products across the EU. **Option B,** while allowing earlier market entry of alternatives, will overall lead to fewer products developed due to the elimination of the market exclusivity. Actions to foster faster generic/biosimilar competition and measures (encourage companies that lose commercial interest in an orphan medicine to sell it to another company; capping the duration of the orphan designation), under **the common elements**, are also going to support better patient access.

On **objective 4**, all options perform in a similar manner. Measures such as providing for more flexible criteria to better define an orphan condition, streamlined procedures for designation and authorisation of orphan medicines, scrapping the orphan designation criterion on the basis of insufficient return on investment and transferring the responsibility for adopting decisions on orphan designations to the Agency are all included in **the common elements**. Furthermore, the introduction of a Global Marketing Authorisation should also lead to a simplification of the system.

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[191] These criteria will identify products addressing HUMN that will subsequently profit from longer or more generous regulatory incentives under the various options.

These measures are intended to embrace scientific advances and provide more effective and efficient processes and procedures.

7.1.2 Efficiency

Table 17 - Overall comparison of the policy options for orphan products in terms of efficiency

Efficiency: comparison of benefits and costs	**Baseline**	**Policy Option A**	**Policy Option B**	**Policy Option C**
Overall costs and benefits	0	+/-	+/-	++
Administrative costs	0	+	+	+
Impact on SMEs	0	+	-	+

Estimated impact compared to the baseline: + + positive, + moderately positive, –/+ neutral, – moderately negative, – – negative and – – strongly negative

As regards the savings and benefits of the various options, **Option A** is the most expensive for health systems/patients due to the introduction of a novel incentive (regulatory data protection vouchers) and the most generous for pharmaceutical industry due to the same novel incentive. It leads to an overall €538m of extra yearly costs to public payers, while generating €279m of extra profits for originators (and a yearly loss of €59m for generic industry[192]). **Option B** creates savings to health systems/patients, but fails to deliver substantial benefits on access and on rewarding pharmaceutical industry for innovation (including HUMN products). It leads to an overall €1.181m of yearly cost savings for public payers/patients, to a yearly loss of €1.199m profits for originators, and profits of €164m for generic industry[193]. **Option C** is the most **cost-efficient**. It will bring some savings to the health systems compared to the baseline (together with the measures to foster faster generic/biosimilar completion under the common elements). At the same time it also brings the most *benefits* in terms of patient access and the development of products addressing HUMN. In monetary terms, the overall impact is €662m of yearly cost savings to public payers/patients, 640m of profit loss to originators and 88m of profit gains for the generic industry.

As regards **administrative costs**, the impacts for companies are expected to derive mostly from the common elements. Savings will come from streamlined procedures for the designation and authorisation of orphan medicines, scrapping the orphan designation criterion on the basis of insufficient return on investment and transferring the responsibility for adopting decisions on orphan designations to the Agency. Concerning the impact **on SMEs**, all **options** are expected to have a positive impact thanks to the common elements and the (additional or graduated) incentives especially for the development of products addressing HUMN (**Options A** and **C**). On the contrary, the abolition of the market exclusivity (**Option B**) is expected to have a negative impact on SMEs as they may find it more difficult and less rewarding to start the development of orphan medicinal products.

7.1.3 Coherence

Table 18 - Overall comparison of the policy options for orphan products in terms of coherence

Criteria	**Baseline**	**Policy Option A**	**Policy Option B**	**Policy Option C**
Coherence	0	+	+/-	+

Estimated impact compared to the baseline + means that the assessment is positive, and – means that it is negative

[192] See Section 6.1.2 for the combined (monetary) impact of the policy options including cost-benefit tables for all stakeholders per option.
[193] Idem.

In terms of **coherence**, all policy options were assessed with regards to their external and internal coherence. As regards the *external* coherence, the interaction of the Orphan Regulation with other EU legislative acts[194] was assessed and its interaction with national plans and strategies. All the three options were considered to be externally coherent. Furthermore, it was also explored how the policy options align with related measures taken at national level by Member States[195]. In relation to these national measures, it was found that significant heterogeneity exists in the state of advancement of national policies, plans, or strategies for rare diseases[196].

Internal coherence mostly related to the interaction with the revision of the general pharmaceutical legislation. Options A and C are internally coherent with this revision as the market exclusivity is kept or modulated under these options whereas Option B is not coherent (due to the elimination of the market exclusivity). Furthermore, all three policy options are internally coherent with the revision of the general pharmaceutical legislation[197].

The current overall system of regulatory procedures and incentives provided by the general pharmaceutical and specific orphan legislation has been considered as 'working in a coherent way' on the basis of the perceived effect by stakeholders interviewed[198]. Furthermore all options are expected to be coherent with external activities and contribute to the achievement of SDG 3 ("health and well-being") and SDG 9 ("innovation and infrastructure").

7.2 Medicines for children

7.2.1 Effectiveness

Table 19 - Comparison of policy options in term of effectiveness – medicines for children

Criteria	Baseline	Policy Option A	Policy Option B	Policy Option C
Effectiveness: contributing to achieving the policy objectives				
Objective 1: Foster investment in research and development of medicines for children	0	+	-	+
in particular for unmet medical needs	0	++	-	+
Objective 2: Create a balanced system for pharmaceuticals in the EU that promotes affordability for health systems while rewarding innovation	0	--	+	+
Objective 3: Increase patient access to medicines for children	0	+	-	+
Objective 4: Streamline processes and reduce administrative burden	0	-	+	+
Effectiveness: other impacts Social impact				
Timely completion of PIPs	0	+	-	+
Number of completed PIPs	0-	+	-	+

Estimated impact compared to the baseline: + + positive, + moderately positive, 0 neutral, – moderately negative, – – negative and – – strongly negative

[194] Regulation (EU) 2018/781 on similarity; Regulation (EC) No 2141/96 on the examination of an application for the transfer of a marketing authorization for a medicinal product; Regulation (EC) No 2141/96 on application for the transfer of a marketing authorization; Council Regulation (EC) No 297/95 on fees.
[195] Nearly all the Member States have adopted a national plan or strategy for rare diseases as of October 2021, except Malta and Sweden.
[196] No data was found to further explore the link between these national plans and the proposed options.
[197] For instance, they both provide a definition for (H)UMNs and create links between specific research priorities and the provision of incentives; they both push for innovations reaching the market more quickly through timely approval and the introduction of an access conditionality; they both simplify regulatory and administrative procedures.
[198] See also Annex 2: Stakeholder consultation (synopsis report).

On objective 1, **Option A** performs best. Thanks to the introduction of novel incentives for products addressing the UMN of children, in parallel to the 6 months SPC extensions for all paediatric products, together with the effect resulting from certain common elements (for example, the waiver system which takes into account the mechanism of action of a product and a better support for early development of UMN products) is expected to results in the highest number of products developed in particular in areas of UMN. At the opposite, **Option B** is expected to result in a decrease of products as the removal of the reward for the completion of the PIP may discourage in particular small companies or academics to start research and development in areas which could be beneficial for children. **Option C**, is expected to result in an increased number of products including addressing UMN of children compared to the baseline, thanks to the action of certain common elements. However to a lower extent than option A, as the reward for products completing a PIP will remain unchanged (6 months SPC extension).

As regards **objective 2**. The affordability of medicines for children depends from the corresponding adult medicines. However, any modification of the length of the paediatric SPC extension, which covers not only the "paediatric" medicine but also the "adult" part of a product , would have an impact on the timing of the generic entry and consequently on affordability. The introduction of additional rewards for products addressing UMN of children in **Option A**, is expected to result in a delayed generic entry for these products and therefore result in the highest impact for the health systems. **Option B** is expected to create savings for health systems compared to the baseline due to the abolition of the reward for the completion of a PIP resulting in an early generic entry. However, it will not ensure that children will be able to benefit of this improved affordability as often generic products do not cover specific paediatric preparations, dosages, pharmaceutical forms. The originator product remains the only available source even after the expiry of the protection period. While the price of originator decrease following generic entry, the lack of competition for certain paediatric formulations and preparations cannot guarantee that affordability will be achieved for medicine for children. **Option C** is expected to result in small improvement for what concern affordability compared to the baseline, thanks to common elements which by reducing the costs related to a PIP (for example by introducing early support for products addressing UMN or simplifying and streamlining the PIP process,) may results in lower prices of the product.

Regarding **objective 3**, the streamlining and simplification of the PIP system and the capping of delays under which PIP have to be completed are expected to result in a faster conclusion of the PIP and indirectly to a faster access for patients for **Options A and C**. In **Option B**, the removal of the rewards for the completion of the PIPs, is expected to counter the positive effect of the common elements as companies may de prioritise paediatric research and development. This may result in longer waiting times for children to get medicines adapted to their needs.

On **objective 4**, the reduction of administrative burden for all options analysed derive from the common elements (simplified and evolutionary PIP). In addition, for **Option A** the introduction of a supplementary reward in term of a voucher or of a supplementary extension of the SPC for UMN product may increase the overall administrative burden for companies and for public authorities. In the case of transferrable voucher, a system to manage the vouchers issues will need to be put in place and companies would be expected to fulfil further administrative requirements compared to the baseline situation. In the case of an extension of the SPC extension for products addressing UMN, in particular generic companies may face further complexity to plan the launch of generic medicines due to the further complexity that will be added to the SPC system.

Social impact: As mentioned in section 6.2.3, benefits for children derive from the avoidance of ADRs and increased quality of life thanks to medicines studied and authorised for specifically for them. However, as the average impact of ADR is relatively mild, even if potentially may result in a thalidomide-like scenario, and it is not possible to anticipate which products will be developed, it is not possible to provide a direct quantitative assessment of these benefits. The social impact is therefore related to the number of new paediatric products developed and to their timely access to patients due to a quicker completion of the necessary paediatric studies. The impact of the options

on the number of medicines for children has already been described under objective 1 above. Concerning the timely completion of PIPs both **Option A** and **Option C**, thanks to the common elements (cap of deferrals and simplification and streamlining of the PIP procedure) are expected to increase a faster completion of the PIP compared to the baseline, resulting to a quicker availability of products dedicated to children. In **Option B**, the removal of the reward for the completions of the PIPs, is expected to counter the positive effects of the common elements as certain companies my no more prioritise studies in children, resulting in later completion of the PIP and less products specifically developed for children.

7.2.2 Efficiency

Table 20 - Comparison of policy options in term of Efficiency – medicines for children

Criteria	**Baseline**	**Policy Option A**	**Policy Option B**	**Policy Option C**
Efficiency				
Overall costs and benefits	0	-	+	0
Administrative costs	0	-	+	+
Impact on SMEs	0	+	-	+

Estimated impact compared to the baseline: + + positive, + moderately positive, 0 neutral, – moderately negative, – – negative and – – strongly negative

Concerning saving and benefits, **Option A** gets the lowest scoring. The introduction of increased rewards for products addressing UMN of children would – on the one side - benefit economically the originator industry (441m gross benefit). On the other side, this would create also much higher costs compared to the baseline for health systems and patients (307 m). At the Opposite, **Option B,** abolishing the reward for the completion of PIPs is the one which is expected to score higher bringing benefits for patients and health systems (1510 m of savings) despite the higher costs for industry (in particular for originators -1756m) which will continue to be obliged to conduct PIP (even more than in the baseline due for example to the introduction of the mechanism of action in the common elements) without receiving any reward for this obligation. **Option C** for what concerns the saving and benefits originating from the paediatric SPC extension is expected to remain overall neutral compared to the baseline as the SPC paediatric extension will remain as in the baseline, the only difference in cost benefits for public authorities and industry will be related to the increased number of PIP and products that are expected to be developed as a consequence of the common elements.

Concerning administrative costs, the impact is expected to come from the common elements so all options are expected to score equality positive in this respect. Nevertheless, the novel rewards intended to be introduced under **Option A** are expected to increase the overall administrative costs for companies and for public authorities.

Concerning the impact on SMEs, **Option A and C** are expected to have a positive impact thanks to the common elements and the rewards granted for the conduction of paediatric studies. The abolition of the rewards on **option B** is expected to have a negative impact in particular on SMEs who may find more difficult to start paediatric development project due to abolishment of financial rewards for conducting clinical studies in children.

7.2.3 Coherence

Table 21 - Coherence

Criteria	**Baseline**	Policy Option A	Policy Option B	Policy Option C
Coherence	0	-	-	+

Estimated impact compared to the baseline + means that the assessment is positive, and – means that it is negative

In terms of *external* coherence the policy options have been assessed against the following initiatives: the SPC Regulation, the clinical trial Regulation, the HTA Regulation, national funding initiatives. Concerning the SPC Regulation, Option A and C, which maintain the SPC paediatric reward, are coherent with Regulation and its ongoing revision. The simplifications and reduction of administrative burden that the SPC revision will bring will be complementary to the ones that will be achieved by the simplification and streamlining of the PIP procedure. The **EU Clinical Trials Regulation**[199] facilitates the conduct of trials in small populations scattered in several MS. Therefore supporting measures of Option A and C in their intent to foster the development of new products in particular in areas of UMN. Option B, with the abolition of the SPC paediatric extension and the possible de prioritisation of clinical research in children by companies, may counter the positive effect expected from the clinical trial Regulation. The HTA Regulation, which is expected to overcome the national HTA procedures diversity, and to reduce their length and complexity in different Member States, is expected to be coherent with all the options

The coherence with the revision of the general pharmaceutical legislation has also been assessed. All the options proposed are coherent with the preferred option selected in the revision of the general pharmaceutical legislation and the two initiatives share similar objectives. In the case of transferable exclusivity vouchers (TEVs) foreseen in Option A, at first glance, there may seem to be incoherence between the two regimes. As in this impact assessment TEVs are considered as an ineffective incentive to generate innovation, whereas in the case of antimicrobials in the general pharmaceutical legislation, they may be a plausible incentive if applied strictly. This different conclusion stems from the 'special' character of the antimicrobial sector and the risk of a high number of TEVs if applied for paediatric medicines. The societal risk of AMR (which potentially concerns the whole population and not just a few patients) and its actual and potential economic consequences combined with the very limited development pipeline of antimicrobials suggests that the advantage of having TEVs specifically for novel antimicrobials may surpass the disadvantages of the high costs for the very limited number of TEVs that are likely to enter the market.

All policy options contribute to SDG 3 ("health/well-being") and SDG 9 ("innovation/infrastructure").

7.3 EU added value and proportionality and subsidiarity

All options for both initiatives bring EU added value for health systems/patients and pharmaceutical industry. All options for both initiatives are consistent with the EU's right to act under the Treaty of the Functioning of the EU (covering public health protection, the single market and the free movement of products within the EU). All options propose actions that will allow the objectives of the revision to be achieved to a greater extent than if Member States were acting alone. Furthermore, all options are proportionate in the sense that they do not go beyond what is necessary to achieve the objectives.

All options pursue the objectives of the revision and provide a clear demarcation between EU and Member State level actions. They do not propose any change to the national health care systems which are in the exclusive power of Member States (Article 168 TFEU), but the measures are expected to facilitate the development of medicines for rare diseases and children.

7.4 Limitations of the comparison

For both legislations quantification has not been possible for several indicators. Therefore qualitative analysis have been conducted. There is also a level of uncertainty in the findings described in this chapter owing to the influence of other contextual factors such as developments in the

[199] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC.

pharmaceutical sector, other relevant legislations (e.g. HTA Regulation, SPC Regulation) and policies at Member State level (e.g. for pricing and reimbursement). Further details are provided in Annex 4 section 3.c.

8 PREFERRED OPTION

8.1 Orphan medicinal products

The preferred option is **Option C**. This option is expected to provide a balanced positive outcome contributing to the achievement of the four objectives of the revision. It is expected to increase the number of orphan medicines compared to the baseline. It will especially refocus investments in products addressing HUMN, without undermining the development of medicines for rare diseases where treatments already exist but where new therapeutic options can still benefit patients and healthcare providers. This will boost research and innovation and would also improve the competitiveness of the EU industry including SMEs. Option C provides a balanced market exclusivity system, also allowing for earlier market entry of (similar) competitor orphan medicines while incentivising products in areas of HUMN. Options C leads to the best results in terms of patient access, due to the proposed access conditionality for the extension of the market exclusivity. The streamlining and the simplification of the procedures (better coordination between scientific committees, transferring the responsibility for orphan designation to the Agency) is expected to result in more efficient procedures and timely authorisation. Furthermore, more flexible criteria to better define an orphan condition will make the authorisation procedures more 'fit' to accommodate new technologies and reduce administrative burdens. The introduction of a Global Marketing Authorisation should also lead to a simplification of the system.

Table 22 - Yearly costs and benefit calculated per interested stakeholder group for preferred Option compared to the baseline

	Cost/benefit for **public payer and patients**	Cost/benefit for **originators**	Cost/benefit for **generic industry**
Option specific measures			
+1 year of ME for HUMN addressing medicines	+€82m additional cost 1-2 additional HUMN medicines per year	+€94m gross profit	- €13m gross profit
1 year of ME conditional for full EU launch	€288m cost saving from non-complying medicines (6 non-complying MP) Broader and faster access to complying medicines	-€282m gross profit loss (6 non-complying MP) +€4m additional cost (4 complying MP)	+€38m gross profit gain due to non-complying medicines (6 non-complying MP)
Common elements			
Day-1 entry of generic/biosimilars after ME expiry	€360m cost saving	-€354m gross profit loss	+€50m gross profit Predictable market entry
Abolishing 2-year ME extension for completing PIP	€96m cost saving legal clarity	-€94m gross profit loss	+€13m gross profit
Global marketing exclusivity	cost neutral, more predictable	Shorter protection time Stronger protection =cost neutral	cost neutral, more predictable
Total balance	**€662m cost saving** **+1-2 additional HUMN** **+9% broader and faster access**	**-€640m gross profit loss**	**+€88m gross profit**

The impact of preferred **Option C** will be complemented by elements of the preferred option and common elements in the revision of the *general* pharmaceutical legislation. In particular:

- The access conditionality, linking 1 year of additional regulatory data protection with effective placing on the market and supply of medicines in all Member States, within 2 years from authorisation, is aligned with the access conditionality of 1 year of additional market exclusivity for medicines for rare diseases. The positive effect on access and availability is expected to be even stronger for innovative and HUMN orphan medicines for which extended market exclusivity and regulatory data protection will be combined.
- Procedures will be simplified and streamlined. Provisions to streamline assessment activities between committees, and pre- and post-authorisation procedures, such as efficient interaction between different legal frameworks (e.g. medical devices) and downstream decision makers (HTA bodies, payers), abolishing renewals, integrating digital tools and real world evidence into the regulatory system and IT-driven processes (e.g. electronic submissions and variations of marketing authorisations) are some of the measures that are expected to reduce burdens and costs for companies and public authorities.

The legal instrument used is planned to continue to be a Regulation.

Competitiveness and future of innovation under reduced market exclusivity

Industry stakeholders claim that the reduction of market exclusivity period would harm future innovation and EU competitiveness. The incentives are agnostic to the geographic origin of the medicines, therefore the reduction would not harm EU companies more than non-EU companies coming to the European market (non-EU companies develop 80% of new medicines introduced to the EU market).

However, lower profits may transform into less innovation at a global scale. Option C estimates a total loss of €640m in gross profits. Industry re-invests on average 25% of their gross profit into R&D, consequently €160m may be lost for innovation. In 2021 the global pharmaceutical industry has invested €230b in R&D, hence the potential loss amounts to 0.07% of global R&D investment. If we wanted to translate this into medicines, only 1 in the next 1500 new medicines would not be developed because of the reduction, a likely invisible loss over the next 15 years.

Taken together with changes proposed in the general pharmaceutical legislation[200], and to the paediatric incentives, the combined effect remains marginal compared to global R&D investments.

8.2 Paediatric medicinal products

The preferred option resulting from the analysis presented in Chapter 7 is **Option C**. This option is expected provide a positive outcome contributing to all the objectives of the revision and results balanced under all the criteria screened.

Option C is expected to yield to an increased number of products in particular in areas of UMN needs of children which are expected to reach children faster than today while ensuring a fair return of investment for medicines developers who fulfil the legal obligation to study medicines in children, as well as reduced administrative costs linked to the procedures that follow from the obligation. The increased costs for public authorities and corresponding benefits for originators correspond to the expected development of more products addressing in particular UMN of children.

All stakeholder groups consulted support option C[201].

[200] The preferred option of the revision of the general pharmaceutical regulation has two variations, depending on the eventual length of the market launch incentive. One variation results in +€298m gross profit, and the other results in -€602m gross profit for the innovator industry.

	Cost/benefit for **public payer and patients**	Cost/benefit for **originators**	Cost/benefit for **generic industry**
Option specific measures			
Maintaining current extension	Cost neutral	Cost neutral	Cost neutral
Common elements			
Mechanism of action	3 more PIPs +€151m cost (1 SPC extension)	+€169m gross profit +€66m cost	-€33m gross profit
Cap in the maximum length of the deferrals	Faster completion of PIPs Cost neutral	Cost neutral	Cost neutral
Total balance	**+€151m cost** **+3 PIP** **+earlier access**	**+€103m gross profit**	**-€33m gross profit**

The positive impact of the preferred option will be complemented by some of the elements of the revision of the *general* pharmaceutical legislation. In particular

- The criteria to identify UMN to be defined in the general pharmaceutical legislation will be the same for medicines for children. Therefore medicines for children identified as addressing UMN will be entitled to any eventual additional regulatory incentives that could be granted to products addressing UMN. It is estimated that such provision will give an additional push to developers. Moreover, the additional regulatory incentives to be provided for products addressing UMN will serve as a "safety net" for a fair return on investment in cases when the SPC reward may not cover all Member States or may be not available (historically, around 50% of the completed PIPs benefitted from the SPC reward).
- Provisions linking regulatory data protection incentives with the effective placing on the market and supply of products medicines in all Member States, within a certain period of time, will also apply to medicines for children. This will further improve patient access to these medicines across the EU.
- Marketing authorisation procedures will be streamlined. This may decrease life-cycle costs for paediatric medicines and may help to ensure that originators maintain paediatric formulations over the entire life-cycle of the adult product and may increase the probability that generic companies copying the adult product will include the paediatric version[202].

The legal instrument used is planned to continue to be a Regulation.

8.3 REFIT (simplification and improved efficiency)

Preferred option orphans: The transfer of the responsibility for orphan designations from the Commission to the Agency is expected to result in simplification and increased efficiency. Furthermore, the abolishment of the yearly reporting for companies on the status of development of their orphan designation will entail less administrative burden. Better coordination between scientific committees will lead to faster assessment of the marketing authorisation application and lower the administrative burden for industry and reduce the number of interactions with the Agency.

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[201] In the public and targeted consultations, industry criticised the introduction of the mechanism of action as a common elements. However, they now support the measure as it brings alignment between the European and the US regulatory system: https://www.efpia.eu/about-medicines/development-of-medicines/regulations-safety-supply/stimulating-the-development-of-new-medicines-for-children/

[202] There is no obligation for generics and biosimilars to adapt their products to children friendly forms

Preferred option paediatrics: Streamlining and simplification of procedures for agreeing a PIP are expected to lower the administrative burden for industry. This is due to the reduced number of interactions with the Agency during the PIP process and to the simplified dossier that will be requited in certain cases. Industry strongly supports the simplification and streamlining of the PIP procedure.

8.4 Application of the 'one in, one out' approach

Orphan medicines: Reduction of the administrative costs for companies (about 3,6 m € per year) will result from preparing slightly fewer applications for an orphan designation and taking away annual reporting requirements. Pharmaceutical companies including SMEs, whose products are designated as orphan medicinal products, will continue to pay *reduced* fees for regulatory activities including for the marketing authorisation[203]. The implementation of the common elements will result in savings. Some of these savings will be offset by a slight increase in administrative costs for pharmaceutical industry due to the creation of a seven-year temporal validity for an orphan designation to stimulate timely product development and application for a marketing authorisation and the variable duration of market exclusivity for eligible products.

Paediatric medicines: A reduction of the administrative costs for companies per PIP will results from the simplification of the PIP procedure and from the new evolutionary PIP system. This streamlined process could affect up to 25-30 % of the procedures. There would be an increased effort for the Agency's Paediatric Committee (+ 10-20 %), but a reduced burden for industry (30%) due also to a better alignment with the US system.

Moreover, a less demanding PIP in the case of the paediatric only products will reduce burden and timing of the PIP preparation and application, including for PUMA products. However, specific impact figures cannot be provided as the number of paediatric only products cannot be anticipated.

An increase of the number of PIP and products is expected under the preferred Options and this has to be factored in the overall yearly administrative costs. The preferred option is therefore expected to result in a yearly reduction of administrative costs of 1,50 m €. Details are provided in Annex 3.

9 HOW WILL ACTUAL IMPACTS BE MONITORED AND EVALUATED

A series of monitoring parameters have been identified to evaluate the impact of the proposed measures on each of the objectives.

Table 23 - Proposed monitoring parameters

SPECIFIC OBJECTIVE	MEASURES OF SUCCESS AND RESPECTIVE MONITORING INDICATORS		DATA SOURCES
1. Promote innovation, in particular for unmet medical needs.	Pipeline of innovative new medicines for rare diseases and children.	• Number of orphan designations including for HUMN • Number of medicinal products for rare diseases and for children authorised • Number of medicinal products for rare diseases and for children authorised to address H/UMN of these populations • Number of PIP agreed on the base of the mechanism of action of the products • Number of PIP addressing UMN • number of pre-marketing regulatory support (scientific advice, PRIME, rolling review) • Number of research program financed by the EU concerning paediatric products addressing UMN	EMA data Data collected from EU research programs
Create a more balanced and competitive system	-Decreased costs for the healthcare	• Number of generic/biosimilar marketing authorisations.	OECD data; DG SANTE Country

[203] Orphan incentives | European Medicines Agency (europa.eu).

that keeps medicines affordable for health systems and patients while rewarding innovation.	system deriving from orphan products). -Faster introduction of generic and biosimilar medicines in Member States.	• Level of pharmaceutical spending per Member State for orphan medicines.	Health Profiles.
Ensure access to innovative and established medicines for patients.	-Timely access for medicines for rare diseases and children accessible in more Member States.	• Time to market in the various Member States of medicines for rare diseases • Time necessary for the completion of every PIP • Number of PIP finalised after the authorisation of the corresponding adult product and delay of the authorisation of the paediatric indication.	International HTA Database INAHTA, EMA data; IQVIA sales data; EMA data
Reduce the regulatory burden and provide a flexible regulatory framework.	-Reduction of approval time for orphan medicines. -Reduction of the time necessary to complete a PIP.	• Number of simplified PIPs agreed • Number of evolutionary PIPs agreed and conducted • Number of innovative study designs, orphan designations • Number of modifications per PIP • Average completion time of PIPs • Change in percentage of authorisation requests of orphan products granted	EMA data

All the data supporting the indicators are already collected at EMA level. They would not result in any additional administrative burden Annual reports on medicines for children are already published by the Commission could be adapted to accommodate the data mentioned above.

While some indicators (like the number of PIPs agreed or the number of orphan designated products) may provide some preliminary trends, only the number and type of medicines authorised will be able to provide a realistic picture if the objectives of the revision have been achieved. Therefore, it should be taken into account that the development of medicines is a long process and the completion of a clinical development plan can take up to 10-15 years. Incentives and rewards exert their effect up to 10 years after the marketing authorisation and the benefit for patients needs to be measured over a period of time of at least 5-10 years after a medicines is authorised.

ANNEX 1: PROCEDURAL INFORMATION

Lead DG, Decide Planning/CWP references

The Directorate for Health and Food Safety (DG SANTE) is the lead DG on the initiative on the Revision of the EU legislation on medicines for children and rare diseases.

The initiative is in the European Commission's Work Programme for 2022, in Annex II: REFIT initiatives, under the heading 'Promoting our European Way of Life'. The initiative has received the validation in the Agenda Planning on the 1 September 2020 (reference PLAN/2020/6688), and the Inception Impact Assessment was published on 24 November 2020.

Organisation and timing

An Inter-Service Steering Group was set up and included the Secretariat-General) Legal Service, BUDG (Budget), RTD (Research and Innovation), COMP (Competition), TRADE, GROW (Internal Market, Industry, Entrepreneurship and SMEs) and the JRC (Join Research Centre). It met 5 times from 30 October 2020 until 18 May 2022.

Consultation of the RSB

A first version of this Impact Assessment Report was submitted to the RSB on 30 May 2022, the meeting took place on 22 June 2022 and the RSB written (negative) opinion was received on 24 June 2022. After the first submission, the Board concluded the following:

1) The coherence and interaction with the general pharmaceutical legislation (and its revision) and other initiatives is not clear.
2) The presented narrative and intervention logic do not clearly describe and link the problems, objectives, proposed measures and their impacts, particularly in the area of availability and accessibility of these medicines.
3) The description and impact analysis of the options is unclear and their costs and benefits are neither well-presented nor compared. Given the apparent small differences between the impacts of the different options, the report does not sufficiently discuss the sensitivity of the impact analysis and how this uncertainty affects the conclusions.

The table below lists the changes in response to the recommendations of the RSB in its first opinion. Besides these modifications, targeted corrections and amendments have been included to address the technical comments provided by the RSB to DG SANTE.

Recommendation of the RSB	Modification in the impact assessment report in response to the Board's recommendations
(1) The report should clarify the links and overlaps with the general pharmaceutical legislation and its upcoming revision. It should be clear how the ambition of the general pharmaceutical legislation is included in this initiative and how the objectives and measures of the two initiatives create synergies and/or trade-offs. The link with other initiatives should be integrated better in the report, e.g. regarding cooperation at global level. Specific research programmes for these medicines and their link to the general development of medicines should be outlined. Based on a clearer problem identification, the report should present a more coherent narrative with clarified specific objectives and better linked measures. It should	Links with the general pharmaceutical legislation and explanations about the interplay have been included throughout the whole document. In particular, the intervention logic and Sections 5 (options) and 6 (impacts) have been amended. The options have been simplified (see also Annex 5 for a full overview of the options) in order to better allow their assessment and comparison and methodology has been aligned to better show the links with the revision of the general pharmaceutical legislation in order to be able to better take into account the impact of that revision on this SWD. This has allowed to better explain the ambitions of the initiatives, synergies and trade-offs that can be gained. Annex 8 has been introduced and further

better explain the enabling framework character of the initiative and that overall progress depends heavily on the effective interplay with other critical measures. This should help to better manage the expectations of the present initiative.	explains the overview of the overall legal pharmaceutical framework and related legal instruments like the SPC regulation. Relevant research programmes have been further outlined. Their link with the development of medicines has been further elaborated in Section 1.3.1 and Annex 8. The problem definition has been streamlined, a detailed problem tree has been added in the report. A full-fletched intervention logic has been added, better showing links between objectives and measures. The enabling framework character of both initiatives (general pharmaceutical revision and revision of the Regulations on medicines for rare diseases and children) have been made clearer, especially in Sections 1.3 and 2.1. The interplay with other critical measures, in particular those outside the competence of the EU and within the competences of Member States (pricing & reimbursement, for instance) has been further explained in Sections 2.1.2 and 2.1.3.
(2) The problems of availability and accessibility of these medicines should be clarified, together with their drivers, substantiated with robust evidence (e.g. EC pharmaceutical sector inquiry), and informed by the views of affected stakeholders. The report should be clear if the problems mainly lie with the Member States or the market behaviour of pharmaceutical industry or result from an economic market failure (e.g. lack of economic incentives). It should also be clear on the relative importance (and possible interaction) of the drivers and at which level these can be tackled most effectively while respecting subsidiarity and Member States competences. Finally, it should be clear what the different specific objectives are regarding availability and accessibility, how they relate to each other, and what the trade-offs are (e.g. higher absolute number of new medicines vs number of patients benefitting from new or less costly medicines).	The problems description has been clarified (see also point 1). The problems related to patient access have been further elaborated and substantiated in Sections 2.1 and 2.2 and have been informed by the views of affected stakeholders. It has also been made clearer what is in the EU's remit and what belongs to the Member States. It has been clarified how the different options and common elements aim to tackle issues concerning development on medicines and access to medicines by patients. The links between the specific objectives have been better outlined.
(3) The description of the options should be clarified, both in content and how the specific measures work together to tackle the problem drivers and reach the specific objectives. The effectiveness of the different measures in tackling the problem drivers and delivering on the specific objectives should be better assessed.	The options have been simplified and their functioning has been adjusted and clarified in Section 5. It has been further elaborated how the common elements work together with the options and how they aim to contribute to the achievement of the different objectives. It has also been assessed how the different policy

The report should clearly demonstrate that the proposed measures are complementary and compatible with the upcoming revision of the general pharmaceutical legislation.	options in tackling the problems and contributing to the achievement of the objectives including in relation to the pharmaceutical incentives under the general pharmaceutical legislation (in Sections 6 and 7). This to also calculate the cumulative effects of those two revisions. The complementarity of the two revisions has been demonstrated by reference to their common objectives (Section 2.2.) and by taking into account the impacts of the options of the general pharmaceutical legislation (Section 5).
(4) The analysis of the impacts should be structured better and presented clearly. The analysis should be understandable for a non-expert reader with cross references between results and calculations. The assumptions should be outlined clearly. The impacts on SMEs should be analysed further and the evidence available for assessing these impacts should be put forward. The report should be clear which measures are most cost-effective.	We have aligned the methodology used for the analysis of the assessment of the impacts (Section 6 and Annex 4) with the methodology used for the impact assessment of the *general* pharma legislation, with the aim to improve clarity, readability and consistency. The assumptions on which the model was based have been further explained and impacts on SMEs have been analysed, where possible. The available evidence on the impacts on SMEs has been presented in Section 6 and Annex 11 (SME test).
(5) The comparison of options should be supported by a clear overview of costs and benefits of the different options and a clear assessment in terms of effectiveness, efficiency and coherence. This should help the selection of a preferred option and in assessing its proportionality. The trade-offs for the different options regarding innovation, availability and affordability should be described, including possible unintended consequences such as earlier or later entering in the market of both innovative as well as generic medical products. Given the apparent small differences between the impacts of the different options, the report should better reflect the sensitivity of the impact analysis to the limitations of data and the modelling assumptions and how this uncertainty may affect the conclusions regarding the preferred options.	Chapter 7 has been improved to present independently and in a more extensive form the comparison of the options under the angles of effectiveness, efficiency and coherence. The trade-offs have also been described while comparing the options. The consequences (trade-offs) of the different options regarding innovation, patient access and affordability have been better described. The different options have been simplified and better described with a stronger focus on the monetary impacts per stakeholder with more significant results per option (avoiding small differences between the impacts).
(6) The report should present more systematically the views of different stakeholder categories on the problems, options and their impacts.	The views of different stakeholders have been systemically presented throughout the various Sections of the report.

A revised version of the Impact Assessment Report was submitted to the RSB on 28 October 2022 for a final opinion. The table below lists the changes in response to the recommendations of the RSB.

Recommendations of the RSB	**Modifications in the impact assessment report in response to these recommendations**
The report does not sufficiently assess the impacts of reduced regulatory protection periods on the sectors' capacity to finance future medicine innovation and international competitiveness.	A dedicated subsection on competitiveness and future innovation is added to section 8.1, on p. 67.
The report lacks clarity regarding safeguards for market access measures.	Section 5.2.1., description of policy options for rare diseases have been complemented, and explanation on the safeguards (and reference to the revision of the general pharmaceutical legislation) has been added to option C on page 32.
Some of the impact analyses are not sufficiently developed.	Several improvements have been introduced in the text: • Price differences and data accuracy – section 2.2.4 on p. 24 • A footnote explains the difference between scientific advice and Horizon Europe funding – section 5.2.2. p. 34 • An explanation on direct and indirect impacts of HUMN incentive is provided in Annex 4 (methodology) – section 3.d p. 104 • More details are added on how the percentage of population served over time is estimated for the options in Annex 4 (methodology) – section 6., p. 113 • An explanation on the concept of economic rent regarding the voucher is provided – section 6.1.1. p. 35 • Access gain is quantified in Figure 6 (p. 49) and Table 22 (p. 67)

Evidence, sources and quality

The Impact Assessment has built on the:

- Joint Evaluation of the Paediatric and Orphan Regulations (published in 2020)[204]

- Participatory workshops bringing stakeholders together to discuss various topics (see Annex 2: Stakeholder Consultation).

[204] https://ec.europa.eu/health/system/files/2020-08/orphan-regulation_eval_swd_2020-163_part-1_0.pdf

- The findings of the study on the economic impact of the supplementary protection certificates, pharmaceutical incentives and rewards in Europe[205].

Extensive stakeholder consultation was organised, with inputs gathered through a public consultation, targeted surveys, an interview programme and a focus group (for more information, see Annex 2: Stakeholder Consultation).

Evidence on costs of research and development was particularly difficult to gather. Public authorities and pharmaceutical companies provided only few responses to the costing survey. Data from published literature was also used.

[205] Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe (2018): https://ec.europa.eu/health/sites/health/files/human-use/docs/pharmaceuticals_incentives_study_en.pdf.

ANNEX 2: STAKEHOLDER CONSULTATION (SYNOPSIS REPORT)

a. Introduction

This report provides an overview of the consultation activities carried out in the context of the *Impact Assessment of the revision of the EU legislation on medicines for children and rare diseases,* the stakeholders and their opinions. These activities are:

- The public consultation (PC), from 7 May to 30 July 2021.
- Targeted surveys, including Options survey and Costing survey both for pharmaceutical companies and public authorities, from 21 June to 30 July 2021 (late responses were accepted until the end of September 2021, due to the summer period).
- Interview programme, at the end of June 2021.
- Focus groups, on 23 February 2022.

The following five key stakeholder groups (identified as priority groups by the EC) were targeted, namely:

1. Public authorities (European Medicines Agency (EMA), national competent authorities incl. ministries of health, health technology assessment (HTA) bodies, 'payers') in particular on topics such as rewards and incentives, regulatory procedures and efficiency, access, pricing and reimbursement.
2. Pharmaceutical companies (including small and medium-sized enterprises (SMEs)) in particular on their experience with paediatric investigation plans (PIPs), incentives and rewards, product development, as well as marketing authorisations.
3. Civil society representatives (e.g., patients, public health organisations) in particular on issues surrounding accessibility and availability, as well as unmet medical needs (UMN) and QALYs.
4. Healthcare providers (e.g., professional associations) in particular on the adoption of mechanism of action (MoA) criteria as well as questions relating to access and availability.
5. Academia/researchers/research organisations in particular on their involvement in clinical and pre-clinical research, scientific development, as well as the concerns linked to defining the current research priorities.

The consultation actions were agreed with the Inter-Service Steering Group in May and July 2021 and have been carried out as planned.

i. Public Consultation

The questionnaire of the PC[206], which was published on the Commission's *Have Your Say website*,[207] was made available in 23 official EU languages. A list of shortcomings identified in the Evaluation of the EU legislation on medicines for children and rare diseases was presented to the PC respondents. These included: (1) insufficient development in areas of the greatest needs for patients; (2) unequal availability, delayed access, and often unaffordable treatments for patients in the EU Member States (MS); (3) inadequate measures to adopt scientific and technological developments in

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[206] Link to the OPC: https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12767-Revision-of-the-EU-legislation-on-medicines-for-children-and-rare-diseases/public-consultation_en.

[207] The published initiative 'Medicines for children & rare diseases – updated rules' on the Have your say website is available at https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12767-Medicines-for-children-&-rare-diseases-updated-rules_en .

the areas of paediatric and rare diseases and (4) procedures which are insufficient and burdensome. In view of this, citizens and stakeholders were invited to share their **views and experiences on the main obstacles** they face concerning treatments for rare diseases and children, on **possible ways to overcome** these obstacles, and **how to future proof the current legislation**.

In total, the PC received 305 responses, 87 of which came from non-governmental organisations, 67 from EU citizens, 39 from company/business organisations, 33 from academia/research institutions, 32 from business associations, 12 from public authorities, four from non-EU citizens, two from consumer organisations, and one from a trade union. As to the representation of SMEs, 12 stakeholders were micro, small and medium-sized companies/business organisations, from eight different Member States.

The remaining 28 responses have been submitted by 'other' stakeholder groups. Overall, 88.8 % of responses came from the EU MS, 3.6 from the US, while 7.8 % came from other countries.

In total, five separate contributions were submitted as part of the consultation activities. This includes position papers by APME (Association of Pharmaceutical Manufactures in Estonia) and Medicines for Europe, Novo Nordisk letter to the European Commission, and RECLIP's (Spanish Paediatric Clinical Trials Network) position on the proposed options.

It should be noted that multiple responses among different respondents that were either exactly the same or very similar were found. For instance, such responses were based on the official position of organisations such as EPFIA, EUCOPE and SIOPE.

ii. Targeted surveys

Options Survey

The Options Survey consisted of targeted questionnaires and was designed to engage with the EU-level and national public authorities, pharmaceutical industry representatives (including SMEs), civil society representatives (e.g., paediatric and rare disease patient organisations), healthcare providers and academia to gather detailed information on their views and preferences on the policy options as well as the costs of developing and marketing specific medicinal products.

In total, the Options Survey received 124 responses. Overall, public authorities were the most represented stakeholder group among the Options Survey respondents (46 %). Among public authorities, the representatives of EMA provided the most responses, followed by national agencies, the European Reference Networks (ERNs), health ministries, public health organisations, and national HTA agencies. Healthcare providers also provided a sizeable number (24 %) of responses. Among these were individual healthcare professionals, healthcare organisations, and one professional association. Academia was also relatively well-represented among the respondents (12 %). Fewer responses came from the pharmaceutical industry (9 %) and civil society (9 %).

Costing Surveys

Two types of Costing Surveys were designed: the *Costing survey for pharmaceutical companies* and the *Costing survey for public authorities*.

The **Costing Survey for pharmaceutical companies** consisted of a *questionnaire* to marketing authorisation holders of paediatric and orphan medicines. The questionnaires aimed at obtaining precise figures on administrative, research and development (R&D), manufacturing and marketing costs incurred specifically in relation to the development of paediatric and orphan medicines to inform the Cost-Benefit Analysis.

Only three responses were received to the Costing Survey from the pharmaceutical industry, namely three multinational pharmaceutical companies based in Europe or US. However, since none of them provided the requested cost elements, only a general qualitative description of the costs incurred, they were deemed insufficient for further analysis. Alternative strategies for the collection of relevant data have been identified, including through the analysis of the data from published

literature (mainly the SWD of the Joint Evaluation and Neez, et al. ("Estimated impact of EU Orphan Regulation on incentives for innovation." - Dolon Report 2020).

The **Costing Survey for public authorities** targeted the representatives of the national competent authorities and health ministries. The questionnaire was aimed at obtaining precise figures on the costs, including staff costs, costs of research subsidies distributed by national authorities, and costs of fee waivers and protocol assistance provided by the EMA. These data fed directly into the CBA.

Seven responses were received to the **Costing survey for public authorities**. These responses primarily contained quantitative information about the costs incurred by the same authorities; therefore, they fed directly into the CBA, and they will not be analysed in the Synopsis Report.

iii. Interview programme

The key goal of the interview programme was to collect in-depth information from the most relevant representatives from the five stakeholder groups on certain elements of different policy options as well as on their economic, social and environmental impacts.

60 interviews were conducted: the **majority (42 %) were with public authorities, 28 % were with the pharmaceutical industry, 13 % with academia, and 12 % with civil society representatives.** The least represented group, due to a low response rate, was the **healthcare providers making up 5 % of stakeholders** in the interview programme.

iv. Focus group

The purpose of the focus group dedicated to **potential changes in the current system of regulatory incentives foreseen under the Paediatric and Orphan Regulations** was to validate the key assumptions about the expected impact of a selection of changes. Five key stakeholder groups participated: civil society, healthcare providers, academia, pharmaceutical industry, and public authorities. The focus group hosted **78 participants**. The most represented groups among participants were **public authorities and civil society**, while a similar share of participants represented healthcare providers, academia and pharmaceutical industry[208]. In terms of public authorities, there were representatives from 17 different EEA countries[209].

Methodological approach

The relevant principles and steps on stakeholder consultations outlined in the Commission's *Better Regulation Guidelines* were followed in designing the consultation strategy. The stakeholder consultation's main steps included designing the consultation strategy, conducting consultation work, and informing policymaking through the preparation of the reports.

As with the PC, the data for targeted surveys was cleaned, where relevant, identical responses and campaigns were identified[210]. While for the targeted surveys, most questions helped to obtain quantitative data, the PC, interviews and focus group primarily gathered qualitative data.

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[208] The options given to the participants were: civil society, healthcare providers, academia, pharmaceutical industry, and public authorities. One participant did not identify with any of the five predefined stakeholder groups in the first Mentimeter question and was therefore named ‘unknown’ when responding to this and subsequent questions raised through this tool.

[209] Austria, Belgium, Cyprus, Croatia, Czech Republic, Finland, France, Germany, Ireland, Italy, Netherlands, Norway, Portugal, Romania, Slovenia, Spain and Sweden.

[210] https://ec.europa.eu/info/sites/default/files/br_toolbox_-_nov_2021_-_chapter_7.pdf.

b. Overview of results from the PC, surveys and interviews

General results

The consultation activities reaffirmed that the main problems affecting the two regulations are closely interconnected. For instance, primarily, the stakeholders highlighted concerns regarding the **insufficient economic interest** from companies and **limited funding for research**. While stakeholders expressed concerns about the **limited capacity of the regulatory framework** within the Paediatric Regulation to foster innovation, they agreed that *both* regulations present significant problems regarding a **lack of science in the definition of UMN**. Some stakeholders (in particular patients and academics) stated issues such as 'economic and operational difficulties', a high rate of waiver and/or deferrals, insufficient rewards and incentives, differences in rules across the EU, as well as limited access and availability of medicines which applied to *both* Regulations.

Paediatric Regulation

i. Paediatric investigation plan (PIP)

During the interview programme, stakeholders (in particular academics and industry) called for smoother and more efficient PIP procedures, better coordination of the committees (particularly highlighted by the pharmaceutical industry) and faster opinion delivery. Regarding the latter point, the stakeholders from the pharmaceutical industry and academia emphasised that while the opinion on a PIP can be delivered in 60 days, in practice, most PIPs are delivered in 120 days.

With regards to the ***deferrals***, results from the interview programme revealed that deferrals were considered needed for ethical reasons, trial recruitment and formulation issues, and for finalisation of toxicological evaluations, as noted by the pharmaceutical industry, public authorities and academia. Some interviewed representatives from public authorities and academia mentioned ways to possibly reduce deferrals. The suggestions included transferable vouchers, tax credits and other factors outside the Paediatric Regulation (improvement of trial preparedness, standardisation of health data and health data records to provide evidence).

ii. Unmet Medical Needs (UMN)

With regard to UMN, the targeted surveys and interviews covered the following subtopics: (1) criteria for UMN, (2) systems to identify UMN, (3) measures to develop medicines for UMN, (4) research and development support to UMN, and (5) novel rewards for products addressing UMN. At the same time, the OPC consulted stakeholders on subtopics (1), (3), and (4). Overall, stakeholders continue to consider UMN a serious issue within the Paediatric Regulation.

With regards to the ***criteria*** to define UMN, **around 80 %** of *all stakeholder groups* participating in the Option Surveys indicated that the **'seriousness of the disease'** and **'no authorised treatment for the disease available'** should be included among the most relevant criteria for defining paediatric UMN, while interviewees and OPC respondents generally considered all criteria[211] important when defining paediatric UMNs. Some interviewees cautioned *'not to define it too narrowly through a legislation'*; other interviewees explained that there is a need for a flexible framework to identify UMN. Importantly, the issue of **appropriate formulation** of products was raised by several interviewees.

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[211] Seriousness of the disease (life-threatening and/or seriously debilitating and/or chronically and progressively leading to a seriously debilitating status). No authorised treatment for the disease is available (therefore, a clear need for any treatment for a disease), and no commonly used method that would not be subject to marketing authorisation is widely available (e.g., surgery). Treatments are already available, but the corresponding therapeutic efficacy and/or the safety would need to be significantly ameliorated. Treatments impose an elevated treatment burden for patients. Available treatments are not addressing unmet medical needs in all paediatric ages (e.g., adapted doses and / or formulations / routes of administrations specific to neonates).

With regard to the systems to identify UMN, the general attitudes revolve around UMN being **difficult to define** (particularly among industry and academia) and that this ought to be done in a **multi-stakeholder approach**. Furthermore, the public authorities consulted in the Options Survey provided some suggestions on mechanisms to *better* identify paediatric UMN: **modifying the system of incentives**, **expanding and better monitoring the off-label use of medicines for children**, and **directly engaging with patient representatives and healthcare providers**.

In the Options Survey, the respondents stated that there is a **need to revise a rewards and incentives system**, create **research-driven funds**, and **modify a waiver system**. In addition, a need to introduce a **possibility to link the six-month Supplementary Protection Certificate (SPC) extension** to the timely completion of a PIP and/or the extension by two years of the market exclusivity for paediatric medicines is not an alternative to the six-month SPC extension was noted.

i. Mechanism of Action criteria

During the consultation activities, various stakeholder groups emphasised the need for paediatric drug development to be driven by the mechanism of action (MoA) via a revision of the conditions for granting a waiver. Such a system was supported by academia (91% of correspondents), civil society (86% in favour), public authorities (84 % in favour), and healthcare providers (80 % in favour), but there was little or no support from the pharmaceutical industry[212]. Multi-stakeholder discussions should be arranged in order to introduce further changes and strategies. With regards to the therapeutic area, the majority of interviewees were sceptical of going outside oncology. The main concerns related with the need for an adequate level of understanding in biology, the need for considering diseases with the same genetic cause and the difficulty of obtaining reproducible data. Only some public authorities considered this possible.

ii. Rewards and incentives

Stakeholders consulted via the OPC, targeted surveys, and interviews considered an **insufficient reward and incentives system** as one of the main problems affecting the development of paediatric medicines for UMN. In the Option Survey, respondents from academia and the pharmaceutical industry argued that a **novel complementary reward should be introduced and/or the existing rewards and incentives should be modified** to make them more effective, proportionate, and flexible in addressing the market failure in both paediatric and orphan regulatory areas.

Stakeholders who provided responses to the Option Survey suggested that these complementary actions could include **modifications in the pricing policy**, which, in their view, should aim to assign economic value to any new paediatric indication derived by new clinical research as well as **innovation and investment in off-patent paediatric developments.** Within OPC, stakeholders suggested designing new solutions based on case studies on how antimicrobial resistance (AMR) research and development are incentivised and expeditated, for instance, through pull incentives as well as establishing negative incentives for companies (under revocation of patent protection) if they do not implement these voluntarily. Further complementary actions, such as early rewards or sharing of the resulting data, were also mentioned.

iii. Research priorities

In the Option Survey, nearly half of the respondents from academia (41 %) stated that the **EC should set future research priorities**, whereas slightly more than a third of the respondents (35 %) thought that they should be set by national health agencies and public authorities.

Some interviewees from public authorities observed that the issue with research, in general, is neither funding nor setting the right research priorities, but rather '*a failure of the demand'*, linked to

[212] Only one response from the pharmaceutical industry was recorded.

failures in clinical research and the issue of a small market. Therefore, improvements to clinical trials and pre-commercial procurement could be useful to address the research and development in specific areas.

iv. Access and availability

In the Option Survey, 60 % of the respondents from civil society and healthcare providers stated that accessibility to paediatric medicines had improved somewhat in recent years[213]. Approximately 23 % of respondents, all from the healthcare providers group, also emphasised that the COVID-19 pandemic affected access to paediatric medicines.

During the Option Survey, stakeholder groups also outlined the main ***barriers*** to the accessibility of paediatric medicines: insufficient public/private investment in research and development for paediatric medicines (25 % of respondents) and strategic commercial decisions by companies (25 % of respondents), followed by national pricing and reimbursement policies (21 %), national drug pricing policies (16 %), and EU-level market authorisation procedures (9 %). Some respondents from the healthcare providers group also outlined that the national procedures for marketing new medicines are taking too much time. Other issues emphasised during the OPC and interview programme by civil society and the EU citizens included lack of access to essential medicines due to shortages, lack of child-friendly formulations, and lack of financial access for newer medicines in some EU countries.

v. COVID-19 impact on paediatric medicines

In the Options Survey, nearly half of respondents (44 %) from all stakeholder groups answered that they encountered **problems affecting paediatric research activities due to the impact of COVID-19**. The impact was most evident as implementation of clinical trials has been paused while the research funding has been reduced. Additional restrictions were further imposed, such as patients' access to hospitals and healthcare services, labs, and face-to-face events. Although only 12 % of the respondents in the Option Survey stated that the pandemic was affecting access to paediatric medicines, during interviews, stakeholders from civil society emphasised that the COVID-19 pandemic had exacerbated the shortage of paediatric medicines and increased the risks of under-cured paediatric patients affected by COVID-19 and its complications.

[213] 32 % of respondents from healthcare providers group emphasised that, in recent years, accessibility had not improved at all or had remained the same.

Orphan Regulation

i. Orphan designation criteria

In general, stakeholders from the pharmaceutical industry emphasised that the **current orphan designation criteria are predictable** and **have been effective** in encouraging the development of products for rare diseases. With regards to the ***prevalence threshold***, a clear message from the consultation programme was that lowering the prevalence threshold would not address UMNs better. As interviewees underlined, products for some rarer diseases (with a low prevalence) are available and while there are none for some more widespread diseases.

With regards to the use of the ***incidence criteria*** for rare cancers and short duration diseases to help focus the development of orphan medicines in areas of UMN, some stakeholders supported the implementation of such criteria; others regarded it as *challenging*. In the Options Survey, slightly more respondents agreed than disagreed with this change (28 % and 25 %, respectively). At the same time, during the interview programme, representatives from academia agreed on the incidence criteria for rare paediatric cancers, and some interviewees from civil society suggested the 'combined use' of both prevalence and incidence to define rare diseases.

With regards to the introduction of a ***cumulative prevalence*** criterion for products with more than one orphan designation, the participants in the consultation programme provided varying views. For example, a new criterion of cumulative prevalence was endorsed by a share of academia and public authority representatives, while other stakeholders from the pharmaceutical industry did not support it. According to the pharmaceutical industry representatives, this was mostly because the developments in more orphan indications and prevalence should not be penalised. They also recognised that the fact that an orphan medicinal product is useful for more than one condition (as happens for cancers) is overall a positive aspect, rather than something to be penalised.

A point that stood out during the interviews was that **the prevalence or incidence criteria for cancers**, according to academia, should *still* define a rare population in the Regulation (including for the tissue-agnostic medicines). Furthermore, representatives from academia suggested the **use of ROI as a criterion in addition to prevalence** (or incidence) and *not* alternatively to prevalence. According to the stakeholder, this would avoid overcompensation. At the same time, public authority representatives suggested considering a threshold (without specifying which one) to possibly prolong the market exclusivity period.

ii. Significant benefit

With regards to ***significant benefit***, different stances were expressed by stakeholders**.** In the Options Survey, the majority of stakeholders from *all* groups (48 %) agreed that **the current rules for demonstrating significant benefit should be modified** to ensure that products provide real benefit**.** Public authorities highlighted that significant benefit should be tightened up and evaluated more strictly, for instance, by requiring proof of clinically relevant effect. Moreover, during the interview programme, public authorities recognised that such rules could be improved as sometimes they are difficult, particularly at the time of marketing authorisation when more robust data are needed, especially in areas such as the following: (i) 'Crowded' areas where there are other treatments available, (ii) Oncology where there are first- or second-line treatments, (iii) Combination therapies, (iv) New formulations that are less convenient for patients, (v) When efficacy and safety could not be compared as at the time of marketing authorisation application, data could be limited, and therefore, it is difficult (and unfair) to compare this limited data with the safety data of another product already on the market for many years, (vi) When the demonstration of significant benefit is based on 'major contribution to patient care'. This sometimes means that previous / available medications may 'harm' patients. In this assessment, it is important to hear the opinion of the patients.

iii. Unmet medical needs (UMN)

With regard to UMN, the targeted surveys and interviews covered the following subtopics: (1) criteria for UMN, (2) systems to identify UMN, (3) measures to develop medicines for UMN, (4) research and development support to UMN, and (6) novel rewards for products addressing UMN. At the same time, the OPC consulted stakeholders on subtopics (1), (3), and (4).

With regards to ***criteria*** to define UMN, many stakeholders participating in the consultation activities confirmed that all proposed criteria are essential. In the Options Survey, the most relevant criteria for defining UMN were **the seriousness of the disease**, **no authorised treatment for the disease is available**, and **no commonly used method that would not be subject to marketing authorisation is widely available**. The pharmaceutical industry suggested that **the ROI criteria can be elaborated further**, and there is a need for **clear guidance on indications and scenarios**. Furthermore, during the interviews, the pharmaceutical industry and civil society considered quality of life as an additional criterion to define UMN.

With regards to the ***systems to identify*** UMN, stakeholders participating in the consultation programme, including the pharmaceutical industry, academia and civil society, tended to agree that the definition of UMN in rare diseases should be **dynamic** and supported the idea of introducing a multi-stakeholder dialogue at a very early stage of the development since the definition varies in content and across different stakeholder groups.

In the Option Survey, three ways to identify unmet needs were proposed[214]. All of the stakeholder groups except for the pharmaceutical industry (45 % of respondents in total) identified ***criteria*** **defining UMN in rare diseases should be established in the EU legislation and detailed in scientific guidelines**, which could be updated regularly as the most appropriate. Public authorities participating in the interview programme specified that such criteria would facilitate work or regulators and make its [*work*] more predictable.

With regards to the **creation of *a list* of UMN**, the conclusion was that the majority of stakeholders see it as *unfeasible*. Civil society specified that such a list could be only valuable for research, while public authorities propose that **a list of 'crowded areas'** would be an easier and more effective option.

iv. Rewards and incentives

Similar to the development and regulation of paediatric medicines, **insufficient rewards and incentives** were outlined as one of the key barriers to developing orphan medicines by most stakeholder groups and pharmaceutical industry in particular during the consultation activities of the OPC, targeted surveys and interviews. All stakeholder groups agreed that the **revision of the current reward and incentives system is needed**.

To revise the current system, respondents from civil society emphasised that the **one-size-fits-all incentive framework is not sustainable** for national healthcare systems. Thus, rewards and incentives should be differentiated**.**

v. Research priorities

Similar to the paediatric Options Survey results, nearly half of the respondents (44 %) from academia, the pharmaceutical industry and public authorities thought that the **EC should be responsible for setting the research priorities**. However, around a third of respondents (31 %) stated that others should be responsible for this task. A frequent suggestion was to involve all

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[214] A list of UMN in the areas of orphan medicines in the EU legislation and updated regularly; A definition of UMN in rare diseases in the EU legislation; Criteria defining UMN in rare diseases in the EU legislation and detailed in scientific guidelines, and updated regularly.

stakeholder groups in the process. Likewise, the interviewees from the pharmaceutical industry sustained a '*more integrated approach for fostering research and development'*, as well as an '*ecosystem*' that drives the '*basic research'* and '*transnational research'*. In this context, according to the interviewees, this '*ecosystem*' could be complemented with an '*additional incentive such as a transferrable exclusivity extension, but only in the context of a broad ecosystem*.'

vi. Scientific developments

During the interview programme, the stakeholders were asked to suggest elements to define 'innovative products'. Some suggestions were provided, including: high therapeutic value, new target (new knowledge about the disease), the product itself (e.g. combinations of antibodies, construct which has several elements), delivery (a new and different way to deliver the medicine) and cure versus care.

When asked whether **orphan designation should <u>not</u> be granted to subsets of common diseases** to avoid unnecessary multiplications of rare diseases out of common diseases, the majority of the Options Survey respondents (76 %) from academia and public authorities' groups agreed with this approach.

During the interview programme, it became clear that **a novel scientific-based approach should be used** to define an orphan condition. However, both public authority and industry interviewees recognised that innovation should also be considered outside the Orphan Regulation, and this should include how to get scientific advice early in the development, how to support trial designs in a better way, how to get evidence from Real World Data (RWD), the role of the regulation in innovation, better capacity building and coordination of expertise at EMA level. Finally, industry representatives deemed there is no need for additional measures for similarity assessment for ATMPs.

vii. Efficient procedures

Around 65 % of Options Survey respondents from academia, the pharmaceutical industry and public authorities supported **transferring the responsibility for identifying medicines for use against a rare disease from the EC to the EMA[215].** Some stakeholders who opposed this change[216] stated that they were *satisfied* with the current system. Around half of respondents agreed that this change would result in decreased administrative burden and more efficient procedures, and around a quarter of respondents said it would *not* make a difference. During the interview programme, public authorities assumed that such a transfer of responsibility would not be revolutionary for the *outcomes* of assessments, as there are very few examples when the COMP opinion is not taken over by the EC.

One of the key takeaways from the interview programme in regard to this topic was that the streamlining of procedures is *not* a matter of changes to the Orphan Regulation, but rather, it is a matter of the general regulatory system as a whole (i.e. this should be addressed within the Pharmaceutical Strategy).

viii. Access and availability

The Options Survey results revealed that more than half of the respondents from healthcare providers and civil society groups (63 %) regarded **the accessibility at least as somewhat improved** since 2017. Concerning the barriers that limit access and availability of orphan medicines, healthcare providers and civil society named **insufficient research and development** (28 %) and **strategic commercial decisions by companies** (20 %), followed by the **national pricing and reimbursement policies** (16 %), **companies' strategic (launch) decisions** (16 %), **national regulations** (14 %), and **EU-level procedures** (4 %).

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[215] With 16 % expressing strong support.
[216] 14 % of the public authority and 22 % of the pharmaceutical respondents.

With regard to potential solutions, the majority of respondents (78 %) and particularly from academia, healthcare providers and public authorities' groups, suggested in the Options Survey encouraging **companies that lose commercial interest in a medicine to offer it for transfer to another company**. However, during the OPC, stakeholders from the pharmaceutical industry emphasised that companies already engage in licensing deals and transfer their products to another company when there is a shared interest on both sides. Respondents to the survey (68 %) also agreed with **fostering competition from generic and biosimilar medicines by ensuring these medicinal products can enter the market a day after the expiry of the exclusivity period**. This was mainly supported by respondents from the academia, healthcare providers and public authorities' groups. However, it should be noted that during the interviews programme, companies (excluding generic companies) did not consider the increase of generic competition as one of the main concerns relating to the development of orphan medicinal products.

The option to introduce **a limit on the validity of an orphan designation to encourage timely medicine development** gained support from a little less than half of the respondents (48 %), mainly from the academia and healthcare providers groups participating in the Option Survey. All stakeholder groups supported the **harmonisation of procedures on the EU-level** regarding orphan medicines development as raised in all the consultation activities.

ix. COVID-19 impact on orphan medicines

Based on the Options Survey responses, most respondents (39 %) stated that they experienced no problems relating to orphan medicines caused specifically by the COVID-19 pandemic. There were some stakeholder groups that did not know / could not answer this question (29 % of respondents from academia and 21 % of respondents from public authorities). This could be due to the fact that the pandemic is ongoing, and the exact impact cannot be quantified just yet. However, a large proportion of healthcare providers (50 %) thought that the pandemic is affecting **access to orphan medicines**, while 18 % of the public authority respondents stated that COVID-19 is affecting **research activities** relating to rare diseases.

In addition to the negative consequences of the pandemic, many stakeholders highlighted '*lessons learned*' and positive takeaways that could be adapted for the future of orphan medicine development. For instance, the interviewees from the pharmaceutical industry noted that **fostering the utilisation of digital tools** and **telemedicine** could be welcome integrations into the day-to-day practice. However, this would necessitate additional resources for public authorities.

c. Overview of results from the focus group

The focus group discussion was structured around the results of the interactive assessment of **six key questions** focusing on the expected impacts of a selection of changes proposed for the current system of regulatory incentives foreseen under the Paediatric and Orphan Regulations.

On the impact on paediatric products, if the 6-month SPC extension was reduced or abolished, respondents were rather divided among those expecting a proportional decrease in the number of all PIPs and paediatrics products (40%) and those who expected no change (36%). The question was linked to the obligation of completing the PIP. The representatives of national public authorities argued that the **current 6-month SPC extension does not take into account cases when the development of a product takes longer**. Despite the frequency of these cases, the obligation remains the same.

Moreover, **the risk of losing the SPC extension seems not to be enough to accelerate the PIP completion (**32 % of the participants agreed, 46% of participants **did not know or thought that this question was not relevant for them** while the smallest but still significant share of participants (22%) disagreed). Difficulties in recruitment and the complexity of PIPs were mentioned as the main obstacles in the completion of PIPs by industry.

Regarding the impact on products addressing unmet need, if the 10 market exclusivity was reduced or abolished, most participants who responded to this question (62%) expected a **proportional decrease in the number of orphan designations and products**. The need to **review and discuss the possibility to revoke certain incentives granted to the manufacturers** under the current legislation if their impact proves inadequate was recognised, while making the distinction between reduction of incentives and their abolishment. Finally, the representatives of public authorities also highlighted that the current Orphan Regulation **enables repurposing of medicines and many of these medicines are not covered by any patents**. Given this, it is particularly important to consider the intersection between paediatric and orphan products.

Nearly half of the participants in the focus group agreed that the risk of receiving a reduced ME incentive would improve the availability of products actor Member States. However, the decisions related to the availability are not fully in the hands of the marketing authorisation holders. In addition, limiting incentives to products addressing areas of unmet needs was not recognised by all as a way to shift the investments of the industry to those areas: on the one hand, over half of the participants who responded to this question (51%) **disagreed** with the assumption that **limiting incentives to products addressing areas of unmet needs would shift the investments of the industry to those areas**. On the other hand, over a third of respondents (37%) agreed that limiting incentives to products addressing areas of unmet needs would shift the investments of the industry to those areas for both paediatric and orphan products.

Finally, participants were asked to identify which of the proposed solutions regarding the support for the development of products in areas of unmet needs they most agreed with. Most respondents (40%) stated that **no new reward or incentive was needed to support the development of products in areas of unmet needs**. In terms of two different types of vouchers proposed, more respondents supported the introduction of transferable regulatory vouchers (36%) over transferable priority review vouchers (24%). It was also noted that the option involving both vouchers might have been selected by some participants if it was presented among the pre-defined options.

Stakeholders generally agreed that the key issue in the current Paediatric and Orphan Regulations is that the existing measures **do currently incentivise the timely evaluation and development of medicines**. Most agreed that the focus should be on creating a **system that can sustain the existing pathways**, **with some additional measures targeting unmet needs**.

Summary of the focus group discussion

All in all, a need for a holistic approach to the revision of the EU legislation on medicines for children and medicines for rare diseases emerged. There is a need to direct more EU and national research funding to the start-up level to simulate the development of new products and their reimbursement, and make sure they reach patients. Most stakeholders agreed that the current system of incentives and rewards should not be abolished or reduced but rather adapted to the evolving priorities and better tailored with additional conditionality. The introduction of transferable regulatory vouchers has received greater support when compared to transferable priority review vouchers. However, the experience concerning these proposed types of vouchers within the regulatory system remains limited; therefore, a lot of questions concerning the risks of overcompensation, exploitation, unpredictability and time constraints have been raised. Thus, in revising the system, stakeholders asked to dedicate a particular attention to mitigating the risk that new incentives could potentially skew competition or result in other unintended consequences. Finally, given the close links between the revision of the Paediatric and Orphan Regulations and the revision of the General Pharmaceutical legislation, which is being carried out in parallel, all stakeholder groups agreed with the need for further consultations in the upcoming year.

ANNEX 3: WHO IS AFFECTED AND HOW?

1. Practical implications of the initiative

For the Orphan Regulation

The planned revision of the legislative framework on medicines for rare diseases is expected to have an impact on patients, payers/health systems and pharmaceutical companies.

Concerning **patients**, benefits derive from more orphan medicinal products accessible in particular in areas of HUMN.

Originators will benefit from simplified procedures with the Agency and more gross profit from the sales of (HUMN) orphan medicinal products developed. Costs mainly relate to gross profit loss due to the access conditionality and faster entry of generics/biosimilars after the expiry of the market exclusivity. In particular, SMEs will benefit considerably from the simplified procedures.

The legislation will result both in costs for payers/**health systems** (due to the extra year of market exclusivity for HUMN) and in benefits (mainly cost savings of the 1-year of market exclusivity conditionality for non-complying medicines; faster entry of generics/biosimilars).

For the Paediatric Regulation

The planned revision of the legislative framework on medicines for children is expected to have an impact on pharmaceutical industry, health systems/public authorities and patients.

Concerning **patients**, benefits derive from the study in children and of new medicines in particular in areas of UMN resulting (thanks for example to the introduction of the mechanism of action provision) in the avoidance of ADRs and increased quality of life thanks to medicines studied and authorised for children. As explained in section 6 very serious ADR due to the off label use of a product are very rare event and cannot be captured with historical data. While the average impact of ADR could relatively mild, a single very rare case of serious ADR would have the potential to create a thalidomide-like scenario. In addition, specifically researched medicines for use in children may result in breakthrough treatments for diseases for which no treatment at all was available, thereby increasing considerably the quality of life of the affected children, beyond the avoidance of ADRs. As it is not possible to anticipate which products will be developed is not possible to provide a quantitative assessment of this effect. Patient are also expected to benefit a faster access to medicines thanks to a faster completion of the PIPs due to the simplification of the PIP procedure and to the cap of the length of the deferrals.

Pharmaceutical industry are expected to develop more products in areas of UMN for children and at the same time benefit from simplified procedures for agreeing with the Agency on the paediatric development plans which they will have to conduct leading to a reduction of their administrative costs per product developed. .

The legislation will mainly results in direct costs for **public authorities** will mainly due to the costs resulting from the rewards that will be allocated to the products developed thanks to the legislation. However, it should be considered that more products for children are expected to consist in savings from avoided hospitalisation and avoided outpatient treatments. Such benefits were calculated in the Joint Evaluation on the basis of products developed and resulted in minor, almost irrelevant impacts and therefore have not been quantified in this SWD, however, as explained above, the use of non-properly tested product in children may result in catastrophic consequences and in a thalidomide like scenario.

2. Summary of costs and benefits

For the Orphan Regulation

I. Overview of yearly Benefits (compared to baseline benefits – million €) – Preferred Option

Description	*Amount*	*Comments*
Direct benefits		
Pharmaceutical companies (originators)	+€94m gross profit due to +1 year of ME for HUMN medicines	
Pharmaceutical companies (generic industry)	+€38m gross profit gain due to non-complying medicines on launch conditionality +€50m gross profit due to predictable market entry ('day-1') +€13m gross profit due to abolishing 2-year ME for completing PIP	
Public payer/health systems and patients	+€288m cost saving from non-complying medicines access conditionality and broader and faster access to complying medicines +€360m cost saving due to predictable market entry ('day-1') +€96m cost saving legal clarity abolishing 2-year ME for completing PIP	
Indirect benefits		
Administrative cost savings related to the 'one in, one out' approach*		
Direct administrative costs savings	**4.5 m** €	Direct cost saving

*Estimates are gross values relative to the baseline for the preferred option as a whole (i.e. the impact of individual actions/obligations of the preferred option are aggregated together); (2) Please indicate which stakeholder group is the main recipient of the benefit in the comment section;(3) For reductions in regulatory costs, please describe details as to how the saving arises (e.g. reductions in adjustment costs, administrative costs, regulatory charges, enforcement costs, etc.;); (4) Cost savings related to the 'one in, one out' approach are detailed in Tool #58 and #59 of the 'better regulation' toolbox. * if relevant*

II. Overview of costs – Preferred option							
		Citizens/Consumers		**Businesses**		**Administrations**	
		One-off	**Recurrent**	**One-off**	**Recurrent**	**One-off**	**Recurrent**
Costs for +1 year of ME for HUMN products	Direct costs				13 m € loss in gross profits (generic industry)		82 m € additional costs

Costs for 1 year of ME condition for full EU launch	Direct costs				282 m € loss in gross profits (originators) 4 m € additional costs		
Costs Day-1 entry of generic/biosimilars after ME expiry	Direct costs				354 m € loss in gross profits (originators)		
Costs Abolishing 2-year ME extension for completing PIP	Direct costs				94 m € loss in gross profits (originators)		
Administrative costs due to increased number of orphan designations					1.3 m €		
Costs related to the 'one in, one out' approach							
Total	Direct adjustment costs	N.A	N.A	N.A	N.A		
	Indirect adjustment costs	N.A	N.A	N.A	N.A		
	Administrative costs (for offsetting)	N.A	N.A	N.A	**1.3 m** €		

(1) Estimates (gross values) to be provided with respect to the baseline; (2) costs are provided for each identifiable action/obligation of the preferred option otherwise for all retained options when no preferred option is specified; (3) If relevant and available, please present information on costs according to the standard typology of costs (adjustment costs, administrative costs, regulatory charges, enforcement costs, indirect costs;). (4) Administrative costs for offsetting as explained in Tool #58 and #59 of the 'better regulation' toolbox. The total adjustment costs should equal the sum of the adjustment costs presented in the upper part of the table (whenever they are quantifiable and/or can be monetised). Measures taken with a view to compensate adjustment costs to the greatest extent possible are presented in the section of the impact assessment report presenting the preferred option.

For the Paediatric Regulation

The figures cited in the tables below illustrate the benefits and the costs under the preferred options in relation for the affected stakeholders. They are based on the assessment of costs and benefits described in Section 6.2 and Annex 4 section 7.

The figures are presented in comparison with the baseline and are average annual costs in m€

I. Overview of benefits (compared with baseline costs) – Preferred Option. Yearly costs		
Description	***Amount***	***Comments***
Direct benefits		
Industry, originators	169 m gross benefit	Benefits deriving from one estimated SPC extension per year
Patients	3 extra PIPs for products addressing UMN of children Faster completion of PIPs and consequently medicines reaching faster children	Not possible to determine the benefits as it will depend greatly from the products that will be developed
Administrative cost savings related to the 'one in, one out' approach*		
Direct Administrative costs savings	**2.8 m**	Administrative savings for companies deriving from the simplification and streamlining of the PIP procedures

II. Overview of costs (compared with baseline costs) – Preferred option							
		Citizens/Consumers		**Businesses**		**Administrations**	
		One-off	**Recurrent**	**One-off**	**Recurrent**	**One-off**	**Recurrent**
Costs for conducting extra PIPs for originators	Direct costs				66 m €		
Cost for delayed generic entry due to one extra SPC paediatric extension granted per year					33 m €		
Costs for public authorities due to the extra SPC paediatric extension granted					1.3 m €		76 m €
Costs for patients			75 m €				

due to the extra SPC paediatric extension granted leading to delayed entry							
Administrative costs due to increased number of PIP conducted					1.3 m €		
Costs related to the 'one in, one out' approach							
Total	Direct adjustment costs	N.A	N.A	N.A	N.A		
	Indirect adjustment costs	N.A	N.A	N.A	N.A		
	Administrative costs (for offsetting)	N.A	N.A	N.A	1.3 m €		

3. Relevant sustainable development goals

III. Overview of relevant Sustainable Development Goals – Preferred Option(s)		
Relevant SDG	**Expected progress towards the Goal**	**Comments**
SDG no. 3 – Good health and wellbeing	Support the research and development of vaccines and medicines for the communicable and non-communicable diseases that primarily affect developing countries, provide access to affordable essential medicines and vaccines, in accordance with the Doha Declaration on the TRIPS Agreement and Public Health, which affirms the right of developing countries to use to the full the provisions in the Agreement on Trade Related Aspects of Intellectual Property Rights regarding flexibilities to protect public health, and, in particular, provide access to medicines for all	
	Strengthen the capacity of all countries, in particular developing countries, for early warning, risk reduction and management of national and global health risks.	
	Achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential	Increase of medicines especially in areas of HUMN and paediatric medicines

	medicines and vaccines for all.	
	By 2030, reduce by one third premature mortality from non- communicable diseases through prevention and treatment and promote mental health and well-being.	
	By 2030, end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases.	
SDG no. 9 – industry, innovation and infrastructure	Enhance scientific research, upgrade the technological capabilities of industrial sectors in all countries, in particular developing countries, including, by 2030, encouraging innovation and substantially increasing the number of research and development workers per 1 million people and public and private research and development spending.	

ANNEX 4: ANALYTICAL METHODS

Given the harmonised revision of the orphan and paediatric regulations together with the general pharmaceutical legislation along the same objectives, the methodology and models largely build on the impact assessment of the *general* pharmaceutical legislation[217].

1. Data sources

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

Literature and document review: we have carried out a targeted literature and document review of academic and grey literature, using specific topics of each policy option, such as access to medicines, to guide our searches. There is a growing body of published literature and analysis reports that studied specific phenomena relevant to aspects of the pharmaceutical legislation. These provide a direct source of facts and figures that we used in our assessments and referenced across the report. Wider literature relevant to newer challenges for the pharmaceutical industry were also reviewed in order to identify future proofing challenges, resilience of supply chains, new manufacturing methods, combination products, digitalisation, new evidence requirements by regulatory authorities and environmental protection.

Secondary data analysis: quantitative data collected along the medicinal product lifecycle was analysed to derive a set of indicators and feed quantitative modelling of various policy scenarios. For problem analysis and baseline, we used data, where available, for the period of 2005-2020 from the IQVIA MIDAS dataset, Informa Datamonitor and Pharmaprojects, EMA's central Marketing Authorisation Application dataset, MRI decentralized / mutual recognition procedures database and EudraGMP.

Key challenges: All methods applied to our research encountered a varying degree of difficulty in relation to lack of quantitative data available in the databases and sources examined. Despite a growing body of literature and evidence in several relevant areas, we did not find enough data to quantify all relevant impacts of every policy measure discussed in the policy options for the future of the legislation. Whenever possible, we have made reasonable assumptions to assess the impacts, but this lack of quantitative data is a key limitation to our analysis.

2. Identifying and selecting significant impact types

We carried out an initial screening of the 35 impact types set out in the Better Regulation toolbox to identify the impacts the study will be reviewing more in depth for each policy block with each policy option. We used findings from the various analytical strands and data sources to identify all potentially important impacts, considering both positive/negative, direct/indirect, intended/unintended as well as short-/long-term effects. Specifically, our screening was based on the principle of proportionate analysis and considered the following factors.

- The relevance of the impact within the intervention logic
- The absolute magnitude of the expected impacts
- The relative size of the impacts for specific stakeholders
- The importance of the impacts for the EC's horizontal objectives and policies

[217] Staff Working Document – Impact assessment on the general pharmaceutical legislation (Annex 4).

- Any sensitivities or diverging views

This screening identified 8 of the 35 impact types as being of most significance for this impact assessment and therefore a deeper assessment was appropriate for the following key impact types:

- Conduct of business
- Administrative costs on businesses
- Position of SMEs
- Sectoral competitiveness and trade
- Functioning of the internal market and competition
- Innovation and research
- Public authorities
- Public health & safety and health systems

3. Modelling changes in market exclusivity vis-à-vis regulatory data and market protection system

a. Protection types and length in a sample of medicines

A basket of 217 products was selected based on IQVIA Ark Patent Intelligence data where the loss of protection (LOP) date was between 2016-2024 in four countries: France, Germany, Italy, and Spain. We chose this sample because in earlier years the regulatory protection system was not fully harmonised due to the legacy of the pre-2005 system. This sample has an additional benefit of having a prospective feature, in that it shows, based on empirical data, the composition of the most recent and also the expected future protection expiries of medicinal products.

In the basket, there have been 26 orphan medicines, and Figure 1 demonstrates how the protection types and lengths vary among them. These tables omit regulatory data and market protection (RP) because in the case of an orphan medicine the 10-year RP protection is matched by the 10-year market exclusivity protection (ME). Despite the same nominal lengths, the ME allows a couple of months longer protection, because it does not allow (yet) generic medicines to apply for authorisation before ME expiry. RP permits generics to start the authorisation earlier, so they can enter the market right after protection expiry.

Figure 10 – Length of protection of orphan medicines by type of protection

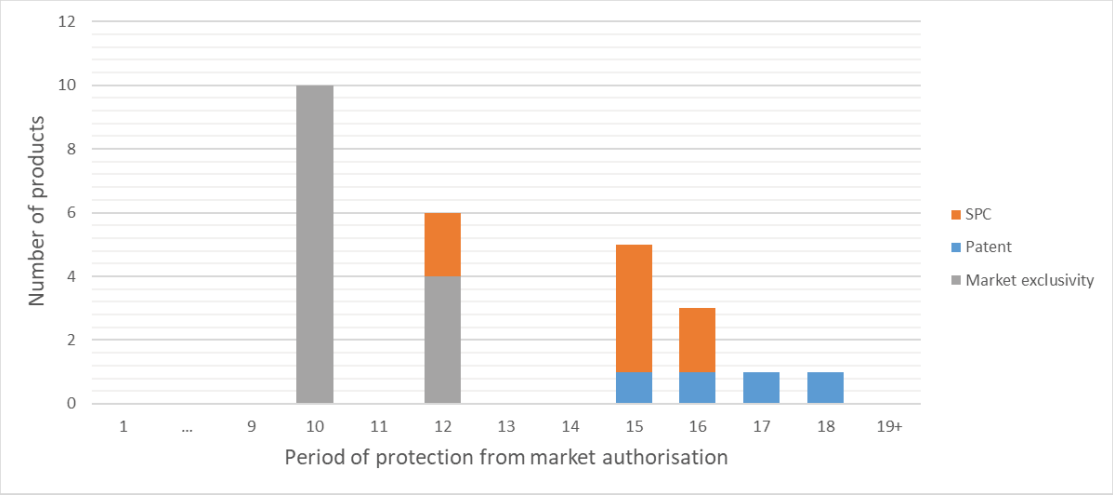


Table 24 - Length and type of protection of orphan medicines

	Years of protection after market authorisation											
Last line of protection	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19+**	**Grand Total**	**Avg peak annual sales**
Market Exclusivity	10		4								**14**	€ 41.4 m
SPC			2			4	2				**8**	€ 475.8 m
Patent						1	1	1	1		**4**	€ 248.0 m
Grand Total	10		6			5	3	1	1		**26**	€ 206.8 m

Similar to the findings of the general pharmaceutical impact assessment, Table 1 demonstrates that SPC and patent protected medicines have a longer protection type, and usually generate higher revenues, whereas products with ME are characterised by shorter protection (10 or 12 years if paediatric studies have been carried out) and lower revenues. In our sample, market exclusivity protected products (14 out of 26) make up more than 50% of all products, but only 11% of the total sales.

Consequently, changes to the market exclusivity (unless making it longer than SPC protections) would not affect SPC and patent protected medicines, thus limiting the economic impacts at systemic level. Nevertheless, changes may have significant impact on certain affected companies.

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

In the general pharma impact assessment a key foundation of the model is a carefully crafted analogue. The analogue takes longitudinal sales data from a basket of medicines that meet certain criteria. For the general pharma this basket was made of RP protected medicines, however orphan medicines with 10-year protection were also eligible for inclusion. The analogue was generated from the weighted and normalised average sales values (in euros) and volumes (in standard therapeutic units) of the medicines in the cohort. To put it simply, the analogue behaves as a typical representative of that basket.

The analogue captures the lifecycle of innovative products over the protected period and that contested by generic/biosimilar medicines after protection expiry. Since ME protected medicines are similar to RP protected medicines in that they also have 10-year protection, and because they have been already included in the general pharma analogue, we have decided to use the same analogue with a slight adaptation. This adaptation is necessary due to the lower revenue generating capacity of non-SPC protected orphan medicines, a different avg. peak annual sales value is needed than in the RP model. After filtering out some very low sales (less than 10M) orphan medicines from the cohort, we have found an avg. peak annual sales of €80 m for ME protected medicines.

In order for sales revenues (euros) and volumes (standard units) across the pre-expiry and post-expiry cohorts and periods can be joined up and compared, aggregate absolute values were normalised so that the originator products' total sales and volume become equal to 100 at one year before protection expiry (Y-1).

A particular challenge is that sales revenues do not give the full picture of company benefits. The driver of businesses economic activity is not the revenue but the profit. Gross profit appears the most adequate and comparable measure, it is the cost of sales deducted from the revenues. The gross

profit only includes the variable costs of manufacturing and distribution, but not the fixed costs, such as R&D and investment in infrastructure. In our model we distinguish three categories of revenues, each with a different margin of gross profits.

- **Protected originator sales**: this is the most profitable category during the protected period of new medicines. Based on a sample of reports from publicly listed companies we apply a 80% gross profit margin on the revenues (20% cost of sales)

- **Contested originator sales**: once generics enter the market, originator products are forced into price competition. Still, originator products can maintain a price premium compared to generics albeit reduced thanks to brand loyalty and strong sales force. We assume a 50% gross profit margin in this category.

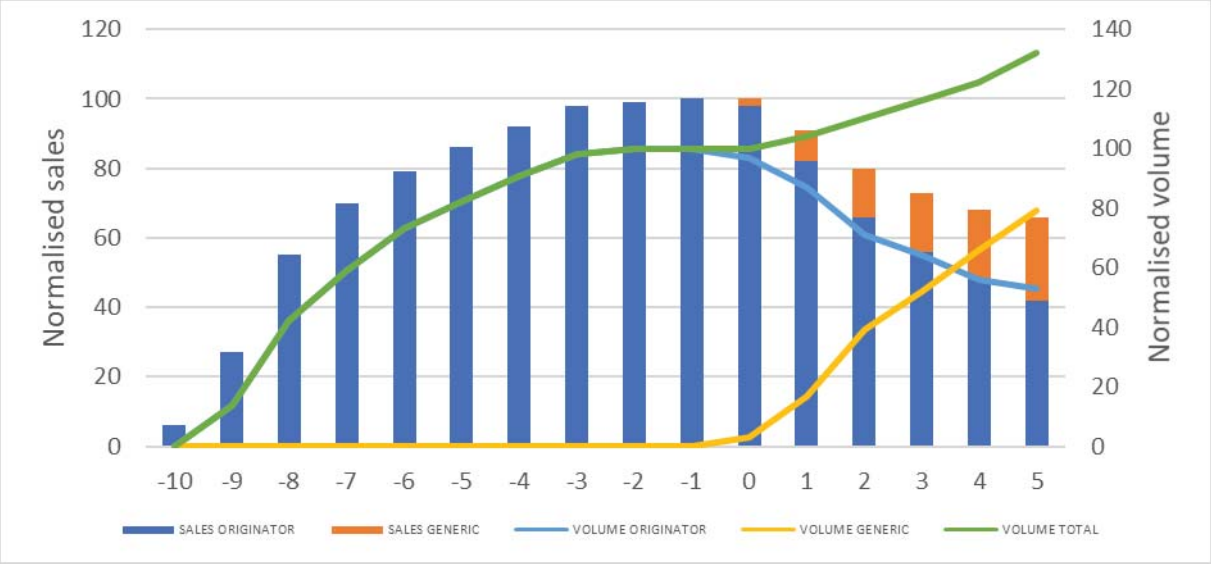
- **Generic sales**: generic industry operates on a high volume, low margin basis. With low product development risk, a lower profit margin can be sustainable. We apply a 33% gross profit margin on generic revenues.

The resulting table and corresponding figure are shown below:

Table 25 - Normalised sales, volume, gross profit and price for products with ME as last measure of protection

Year from expiry	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0	1	2	3	4	5
Originator sales	6	27	55	70	79	86	92	98	99	100	98	82	66	56	48	42
Generic sales											2	9	14	17	20	24
Total sales	**6**	**27**	**55**	**70**	**79**	**86**	**92**	**98**	**99**	**100**	**100**	**91**	**80**	**73**	**68**	**66**
Originator volume	0	14	42	59	73	82	91	98	100	100	97	87	71	64	56	53
Generic volume											3	17	39	52	66	79
Total volume	**0**	**14**	**42**	**59**	**73**	**82**	**91**	**98**	**100**	**100**	**100**	**104**	**110**	**116**	**122**	**132**
Originator profit	4.8	21.6	44	56	63.2	68.8	73.6	78.4	79.2	80	49	41	33	28	24	21
Generic profit											0.66	2.97	4.62	5.61	6.6	7.92
Originator price		1.93	1.31	1.19	1.08	1.05	1.01	1.00	0.99	1.00	1.00	0.94	0.93	0.88	0.86	0.79
Generic price											0.67	0.53	0.36	0.33	0.30	0.30
Average price		1.93	1.31	1.19	1.08	1.05	1.01	1.00	0.99	1.00	1.00	0.88	0.73	0.63	0.56	0.50

Figure 11 - Normalised sales and volume for products with 8+2 years of RP protection (baseline)



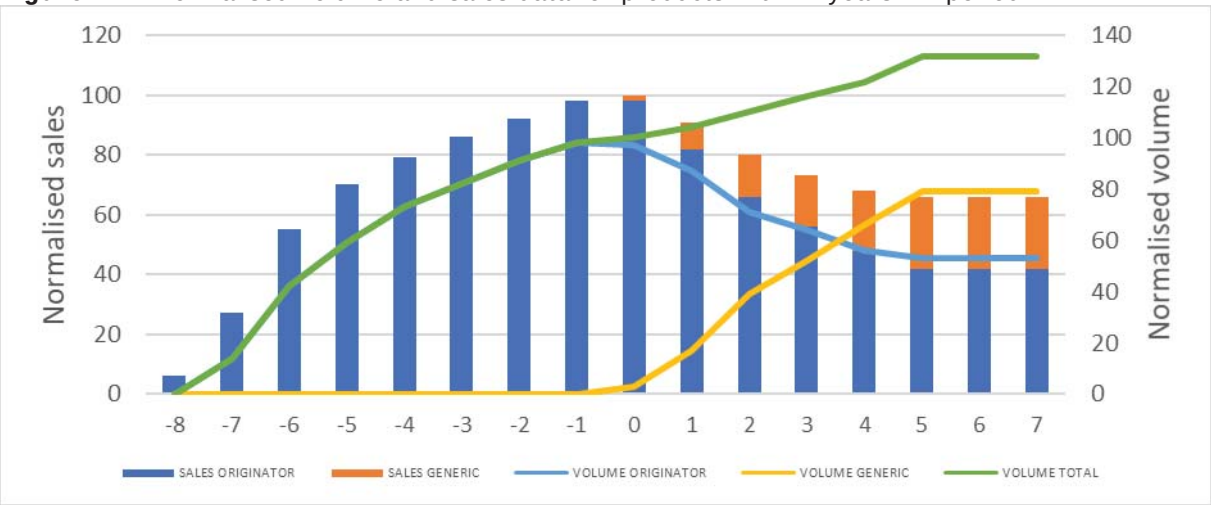
It is evident from the graph that sales revenue and volume grow year-on-year over the 10-year RP period as (i) the product is taken up by the health system and make it accessible to increasingly more patients; and (ii) product is launched in increasingly more member states. It should be noted that health systems may require a number of years before the product becomes accepted by health professionals and routinely prescribed. However, these effects are expected to reach a plateau within a couple of years of introducing the product in a market, and indeed the figure shows that by Y-3 sales figures are close to peaking. The last year before expiry therefore accounts for 14% of total protected sales; while the final two years account for 28% of total protected sales.

c. Modelling the economic impact of decreasing regulatory protection

Some options and common elements include a reduction of the length of market exclusivity. Because even in the revised general pharma regulation the RP would ensure a minimum 8-year protection for all medicines, the maximum lost protection due to shortened market exclusivity is 2 years. This will be the new scenario for the analogue. In the model, we assume that after 5 full years of generic competition an equilibrium value of annual sales and volume of product sold are established and thus we can use Y5 data for originator and generic products as long-term level to calculate the value of ME loss over the product lifetime.

We also assume that the pre-expiry sales trajectory is not changed by company behaviour and thus the baseline Y-1 and Y-2 sales are lost under the new standard ME regime. In the figure below thus the original Y-1 and Y-2 values are removed and Y6 and Y7 values are added at equilibrium level. In addition, we assume that the market dynamics of generic competition (between Y0 and Y5) in the new standard ME regime will not change compared with the ME period of 10 years.

Figure 12 - Normalised volume and sales data for products with -2 years ME period



	Baseline	-2 years ME	change	change %
Originator protected sales	712	513	-199	-28%
Originator contested sales	392	476	84	21%
Originator profit	765.6	648.4	-117	-15%
Generic sales	86	134	48	56%
Generic profit	28.38	44.22	16	56%
Cost to public payer	1190	1123	-67	-6%
Volume (patients served)	1343	1407	64	5%
Cost of additional patients	0	44	44	
Cost of baseline volume	1190	1079	-111	-9%

Using the above model for the product lifetime, we can make the following observations at product level:

- Originator companies' pre-expiry sales loss of -199 (normalised units) over two years is partially compensated by the post-expiry gain of +84 (calculated at the equilibrium level) over two years, giving a net loss of -115 (normalised units) over the lifetime. In other words, originators lose 28 % of their protected sales when the protection is shortened by 2 years. This translates to a decrease in originator's gross profit of -117 (normalised units), which is a 15% loss over the product lifetime, approximated as a 16-year period.

  We know that pharmaceutical industry is one of the most R&D intensive sector and they reinvest a large share of their revenue into innovation for new products and technologies. This share is 20% on average globally[218] and we can assume that the revenue loss will translate to a loss of innovation budget and thus a loss of development of new innovative products and/or incremental (i.e. cheaper) product innovation (e.g. for combination products or new formulations).

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

- Generic companies' start to benefit from sales two years earlier compared to baseline, and thus reach equilibrium level two years earlier. These two extra years of equilibrium generic sales of +48 (normalised units) are equal to +16 (normalised units) gross profit gains.
- Healthcare payers pay less overall due to a decrease in the average price they need to pay for a standard unit of the product. In the baseline 10-year ME regime, the total lifetime sales is 1190 (normalised units) and in the new 8-year protection regime the same volume at the new prices would be 1079 (normalised units). Thus in the new situation healthcare payers would pay -111 (normalised units) less, which is -9% less when considering the lifetime sales of the product.

  In the real situation, however, healthcare payers may not realise this nominal saving but choose to purchase more units of the medicine at a lower price for the healthcare system and expand coverage of patients. This can be considered that payers 'reinvest' part of the savings in the same market and increase purchase of generic products at higher volumes for the benefit of the patient. We can thus calculate the total real sales of originator plus generics product volumes, which can be used to monetise patient benefit. Under the baseline situation, total sales value over the product lifetime is 1190 (normalised units), while under the 8-year protection regime it is 1123 (normalised units), equating to -67 (normalised units) or -6% saving to healthcare payers, on the products that are ME protected. Note, however, when considering the ME protected medicines represent less than 5% of the pharmaceutical expenditure, and that from the total healthcare systems spending in the EU, the pharmaceutical expenditure represents less than 20% (see Analytical report Figure AFF-3, OECD Health Statistics), the savings at the healthcare system level would be marginal.

- Patients benefit due to the increased volume of the medicine sold after ME expiry (2 years earlier) which then reach more patients creating higher level of health benefits. In the model, the total volume increases as soon as generic products enter the market and volume of generic products surpasses that of the originator product by year 4 after generic entry. In the new regime the total volume sold increases by +64 (normalised units) or 5% over the product lifetime above the baseline of 1343 (normalised units) under the 10-year ME regime. However, the extra volume of products available to patients manifest itself in the transition period between expiry and reaching the equilibrium value.

i. Monetising the systemic effects for protection loss due to abolishing ME (Option B)

Option B would result in a 1-year protection loss for orphan medicines that are launched in all EU countries and a 2-year loss for those that are not, because of the revised regulatory protection in general pharma. In accordance with baseline projections, we expect 10 orphan medicines annually where the market exclusivity is the last layer of protection of these, we expect that 4 would comply with market launch in all Member States and 6 would not. Table 7 shows the economic impacts per stakeholder.

Table 26 – Economic impact of no market exclusivity in combination with changes of regulatory protection

	Product level change 1 year loss	Product level change 2 years loss	Systemic change (4 all-EU launch, 6 not all-EU)
Originator gross profit	**-€47m**	**-€94m**	**-€751m**
Generic gross profit	**+€6m**	**+€13m**	**+€101m**
Cost to public payer	-€27m	-€54m	-€430m
Δ of patients treated (monetised)	+€21m	+€35m	+€295m

Patients + payer monetised gain/loss	**+€48m**	**+€89m**	**+€725m**

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

Option B would generate an annual €430m savings to public payers, and with the additional patients served thanks to earlier price competition, the public saving amounts to €725m a year (over the annual €40-50bn that the EU spends on orphan medicines). Apart from supporting affordability, this option also contributes to improving access by allowing the incentive introduced in the general pharmaceutical legislation to affect orphan medicines.

For developers of orphan medicines, the direct impact of abolishing the incentive would be €751m in lost profits. This impact would be amplified by the message transmitted to patients, researchers, companies and investors active in the rare disease area. Divestments and shifting research priorities would likely withdraw resources from orphan medicines development and would be negatively perceived by all stakeholders.

ii. Monetising the systemic effects for protection loss due to not launching in all EU markets (Option C)

Option C offers the same market exclusivity period for standard orphan medicines as the baseline, 10 years, but only if the medicine is launched in all EU markets within 2 years of authorisation. If not launched in all markets, the protection period is 9 years. This aims to motivate companies to launch in all EU member states, and not to leave out small markets, which are not attractive enough commercially. Similarly to the general pharma revision, it is expected that some medicines will not comply with the access incentive conditions. Given the lower level of baseline compliance of orphan medicines reliant on ME compared to non-orphan medicines reliant on RP, the gap to be bridged will be larger. The assumption is therefore made that 40% of orphan medicines will comply (for non-orphans it is 50%[219]), and 60% will not. Thus, of the 10 orphan medicines expected to have ME as last line of protection, we expect that 4 would comply with market launch in all Member States (and 6 not).

If a standard orphan medicine is **launched in all EU member-states**, the reward will have the same economic impact as in the baseline, with the 10-year market exclusivity protection.

No distinction is made here between HUMN and non-HUMN ME-reliant orphan medicines (the total of 10 includes both), since in either case, the length of protection will be increased by one year if the access conditionality is met as compared with those that do not comply. The table below therefore accounts for both cases. Using our model, the impact of 1-year less protection in case of non-launch in all Member States is the following:

Table 27 – Impact of change of -1 year market exclusivity in case of non-launch in all MS

	Product level change	% change	Systemic change (6 medicines)
Originator gross profit	**-€47m**	**-7.7%**	**-€282m**
Generic gross profit	+€6m	+28%	+€38m
Cost to public payer	**-€27m**	**+2.9%**	**-€162m**
Δ of patients treated (monetised)	+€21m	+2.4%	+€126m
Patients + payer monetised gain/loss	+€48m	+5.0%	**+€288m**

[219] General pharma IA SWD, Section 8.1.

For the public payer/patient this instrument is a win-win, if medicines comply, timely access across the EU will increase, and if not, the protection period decreases, lowering cost for society by 48m. The decreased protection translates to 47m lower gross profit per medicine, or 282m for the whole innovative industry.

iii. Monetising the systemic effects for protection loss due to allowing day-1 generic entry (common element)

Allowing entry of generic medicines as soon as market exclusivity is expired, means that an **application for authorisation** of a generic version of the medicine **can be submitted** during the protection period, and can enter the market right after expiry of the market exclusivity. Currently, generic versions of orphan medicines cannot start the authorisation process before the market exclusivity expires[220]. This creates a windfall protection of at least 9 months beyond the 10 years ME, equal to the time needed to authorise a generic medicine from submission[221]. It is estimated that 10 out of the expected 25 new orphan medicines would be impacted per year, the ones where ME is the last layer of protection. Apart from legal certainty for generics it would mean up to €360m savings to the public. Originators would lose their windfall profits by €354m. See Table 11 for the financial impacts of day-1 entry of generic medicines on all stakeholders.

Table 28 – financial impacts of day-1 entry of generic medicines	**Systemic change (10 medicines)**
Originator gross profit	**-€354m**
Generic gross profit	+€50m
Cost to public payer	**-€200m**
Δ of patients treated (monetised)	+€160m
Patients + payer monetised gain/loss	**+€360m**

iv. Monetising the systemic effects for protection loss due to abolishing paediatric ME extension (common element)

Abolishing the orphan market exclusivity extension[222] for completing PIPs will better regulate a system that is currently not functioning very well. At present, the paediatric regulation offers 6 months of SPC extension for completing a PIP, and for orphan medicines 2 years of market exclusivity extension. However, there are several SPC protected orphan medicines with 13-14-15 years of protection duration[223]. Obviously, for these products a 10+2 years market exclusivity is of less value and they would be better off with a 6 months extension of the SPC protection. To switch to this protection, they need to renounce their orphan designation and they often do so. The abolition of the paediatric extension of market exclusivity is thus expected to improve clarity in the system.

Table 29 – Impact of abolishing 2 years ME extension for completed PIP	**Systemic change (1 medicine)**
Originator gross profit	**-€94m**
Generic gross profit	+€13m

[220] See also Section 5.2. of this SWD (common elements).
[221] This is different to the general pharma legislation, where regulatory data protection is designed in a way to allow generic filing before expiry.
[222] This measure is regulated in the Paediatric Regulation and it is mentioned as a common elements of the revision of the paediatric legislation, however it changes the market exclusivity period, therefore its impact is relevant for orphan products therefore it is discussed in this section.
[223] See also Table 3 (length of protection of orphan medicines by type of protection).

Cost to public payer	**-€54m**
Δ of patients treated (monetised)	**+€42m**
Patients + payer monetised gain/loss	**+€96m**

The measure will also imply that orphan medicines not protected by SPC but eligible to complete a PIP, will lose the 2-year extra market exclusivity protection available in the baseline. However, from the entry into force of the Paediatric Regulation up to 2020, only 11 of these market exclusivity extensions were granted[224], meaning that it has been a rarely used incentive. With 1 such incentive not granted per year in the future, the public would save €96m per year. The affected originator companies would lose €94m in gross profits over the medicine's lifetime each, but due to the few uses, the impact on the whole industry is not significant.

Caveats to the model used:

Data: IQVIA MIDAS data includes sales revenue data corresponding to list or ex-manufacturer price without accounting for rebates or discounts (especially in hospital sector) on the one hand and costs including wholesale, distribution, value-added tax and social security expenses on the other to healthcare payers.

Opportunity cost: We present data at current euro level without inflation or cost of capital / commercial risk accounted for. This latter is a factor for commercial actors where monetary gains and losses are normally discounted in business calculations and may change decisions related to product developments accordingly. In contrast, healthcare payers pay on an ongoing basis.

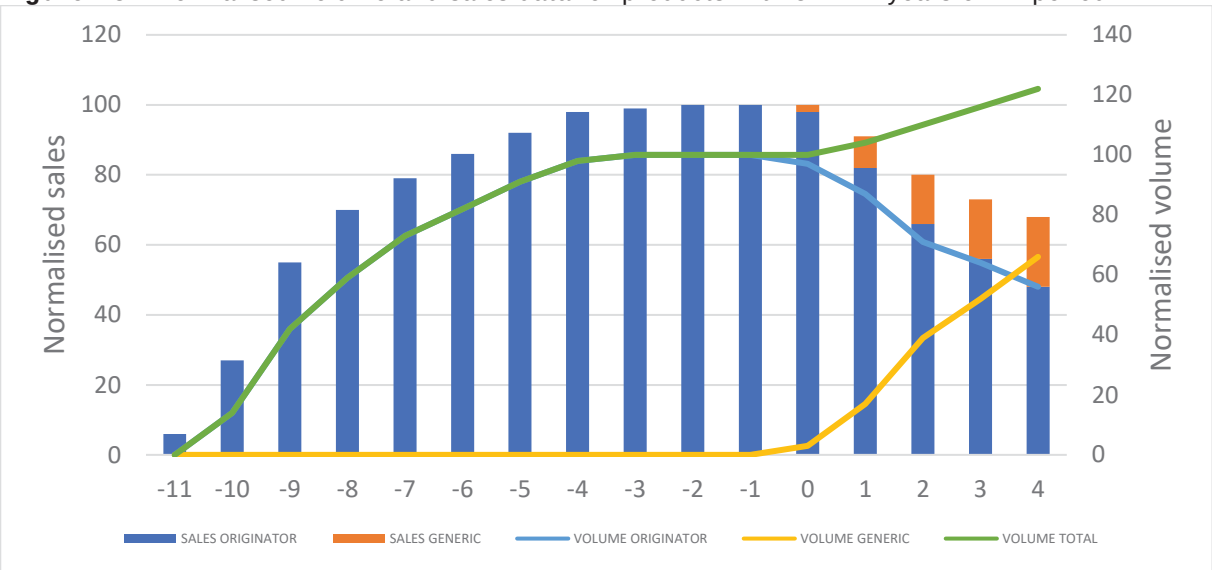
Business behaviour: There may be changes in the trajectory pre- or post-expiry compared to the current RP 8+2 regime, because companies change behaviour and aim to earn similar level of total pre-expiry monopoly rent during the reduced RP period. This may be achieved by entering more markets earlier leading to the same pre-expiry overall sales and volumes of product sold. There is however the risk that the shorter RP period will lead to higher negotiated prices and relatively lower volumes of product sold in the pre-expiry period, or even a reduction in the number of products that enter EU markets.

d. Modelling the economic impact of increasing market exclusivity protection

We use the same data as presented above and assume that after the Y-1 there will be an additional year of peak sales protected by a 1-year ME period. We will use the result of this model to estimate the proportionate effect of the 1 year incentive for HUMN addressing medicines. We assume that pre-expiry sales trajectory is unchanged, the market dynamics of generic competition post expiry is unchanged. In the figure below thus data associated with a new Y-1 is added and the baseline Y5 is removed to maintain the overall product lifetime of 16 years.

[224] EMA data.

Figure 13 - Normalised volume and sales data for products with 8+2+1 years of RP period



	Baseline	+1 year ME	change	change %
Originator non-contested sales	712	812	**100**	14.0%
Originator contested sales	392	350	**-42**	-10.7%
Originator gross profit	765.6	824.6	**59**	7.7%
Generic sales	86	62	**-24**	-28%
Generic gross profit	28.38	20.46	**-7.9**	-28%
Cost to public payer	1190	1224	**34**	2.9%
Volume (treated patients)	1343	1311	**-32**	-2.4%
Patients + payer monetised gain/loss	1190	1241	**51**	4.3%

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

Using the above model for the product lifetime, we can make the following observations at product level:

- Originator companies increase pre-expiry sales due to additional year of monopoly sales by 100 (normalised units) or 14% of lifetime protected sales. In terms of gross profit, this is 47 more monetised unit, or a 7.7% increase.
- Generic companies' start to benefit from sales one year later, and thus generic sales are reduced by 24 (normalised units), and gross profit is reduced by 8 (normalised unit) which is equal to a reduction of 28% sales, compared to baseline.
- Healthcare payers pay more overall due to an increase in the average price they need to pay for a standard unit of the product. We consider again the 'peak' volume sold of the originator product pre-expiry in baseline and use the average price in each year under the different RP regimes to calculate sales. The total cost for healthcare payers is thus -51 (normalised units) over the product lifetime compared to baseline
- Patients lose -32 (normalised units) in decreased volumes of the medicine over the lifetime of the product compared to baseline

i. Monetising the systemic effects for 1-year ME extension for medicines addressing HUMN (Option C)

In accordance with baseline projections, we expect that from the 10 orphan medicines annually where the market exclusivity is the last layer of protection, this measure would affect 20% or two products, which would address HUMN and therefore be eligible for the extra year.

Table 30 – Impact of change of +1 year market exclusivity protection

	Product level change	% change	Systemic change (2 medicines)
Originator gross profit	**+€47m**	**+7.7%**	**+€94m**
Generic gross profit	-€6.5m	-28%	-€13m
Cost to public payer	**+€27m**	**-2.9%**	**+€54m**
Δ of patients treated (monetised)	**-€14m**	-2.4%	**-€28m**
Patients + payer monetised gain/loss	**-€41m**	**-4.3%**	**-€82m**

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

We estimate that an average orphan medicine addressing HUMN and relying on market exclusivity as last line of protection will be able to generate €47m more profit (or 7.7% more than in baseline). Such medicines will become more attractive commercially for developers, and their proportion among the newly authorised medicines would increase. We estimate that instead of the 75 projected HUMN addressing orphan medicines in the dynamic baseline (Section 5.1), there would be 80-85 HUMN products authorised in the next 15 years.

The cost of a +1 year protection for HUMN protection would be shared among generic industry, health payers and patients. With 2 of such incentives annually, the generic industry would lose €38m in revenues a year, which translates into €13m decrease in gross profits. The health payers would need to pay €54m more on an annual basis. The model also accounts for the patients that would not be served due to the higher prices that result from extended protection. Accounting for that effect too, the cost for the public would rise by €82m annually.

Apart from the monetary impacts stemming from the increased market exclusivity period, we also estimated the number of additional medicines coming to the market. The incentive has two effect: (1) it generates more resources for innovators, (2) it makes the EU market more attractive to medicines that otherwise would not come to the market (there are several orphan medicines annually that are only launched in the US market and not in the EU). As a result of subtle and complex effect pathways, we could not identify directly available literature evidence or model. F

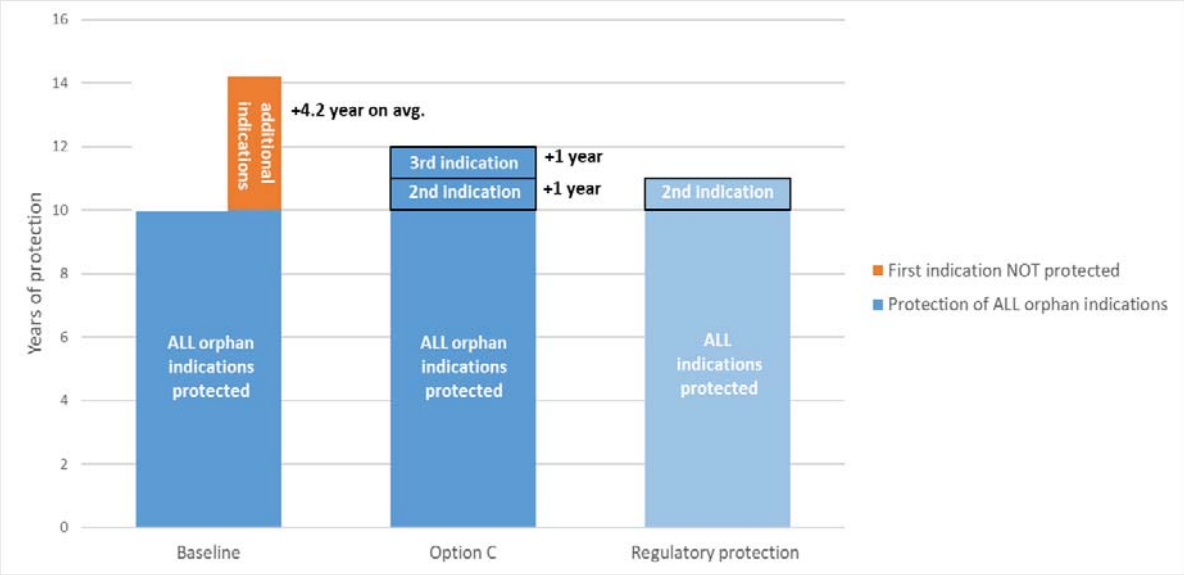
4. Global marketing authorisation

The introduction of the global marketing exclusivity (GMA) will limit stacking market exclusivity periods for additional orphan indications. GMA prolongs the existing market exclusivity by only 1 year in all orphan indications. The use of this incentive is maximised at two indications, i.e. maximum 2 years of prolongation of the ME will be possible. Furthermore, market exclusivity granted **to a second generation product** that is similar to the first generation product will not be applied in respect of generic products of the first reference product for which the market exclusivity expired to avoid so called evergreening[225].

[225] See also Section 5.2 of this SWD.

The GMA would concern 16% of orphan medicines, those with multiple orphan indications. For them it would mean replacing 4.2 years of partial protection for additional indication with on average by 1.3[226] years complete protection of the medicine. Importantly, this would put a limit on 'orphan blockbusters' with several indications, and disincentives on gaming the system for artificially inflated protection periods.

Figure 14 – protected indications under GMA and RP



5. Regulatory data protection vouchers

Overview

Option A envisages a transferrable regulatory voucher as an incentive for originators of products that address high unmet need (HUMN) in rare diseases and diseases in children. The voucher would grant a one-year RDP extension for one medicine. The company awarded the voucher would be allowed to sell on the voucher to another company. For the voucher to be of value, the purchaser must hold a medicine that is reliant on RDP as last line of protection. For products where the SPC or patent expires a year or more after RDP, such a voucher would be of no value.

This section sets out the methodology used to calculate the impact of a voucher scheme for various stakeholders. The analysis highlights the key shortcoming of this form of incentive, namely that the rent generated by the voucher will be shared between the voucher seller and the voucher buyer. Moreover, as the number of vouchers issued increases, the share of the seller declines very quickly. However, the reward to the seller is the intention of the scheme. The reward to the buyer is a by-product. Vouchers come at a significant cost to public authorities, who have to a protection premium on the medicines that use them for an additional year. The more of that additional expenditure that goes to the buyer rather than the seller, the less efficient the scheme.

[226] The weighted average of protection for medicines with one or more additional indication

The methodology set out below aims to simulate the economics of a market for vouchers on the basis of real world data and thereby estimate the shares of voucher rent that would accrue to buyers and sellers respectively. It results in the conclusion that the scheme would become highly inefficient given the number of vouchers that would have to be issued for HUMN products for rare diseases alone (3-6 per year) and all the more so if they were also issued to reward UMN products for children (5-6 per year). As well as being inefficient, such a scheme, by overloading the market with vouchers, would undermine the efficiency of any future scheme to award vouchers for novel antimicrobials. This class of products would be better adapted to this form of reward as it would entail issuing one – or at most – two vouchers per year.

As well as being costly to public authorities, RDP extension vouchers, by delaying the decrease in the price of those medicines, delay the increase in their uptake, which comes at a price to patients. This effect is measured along with the additional cost to public authorities in the calculations set out below.

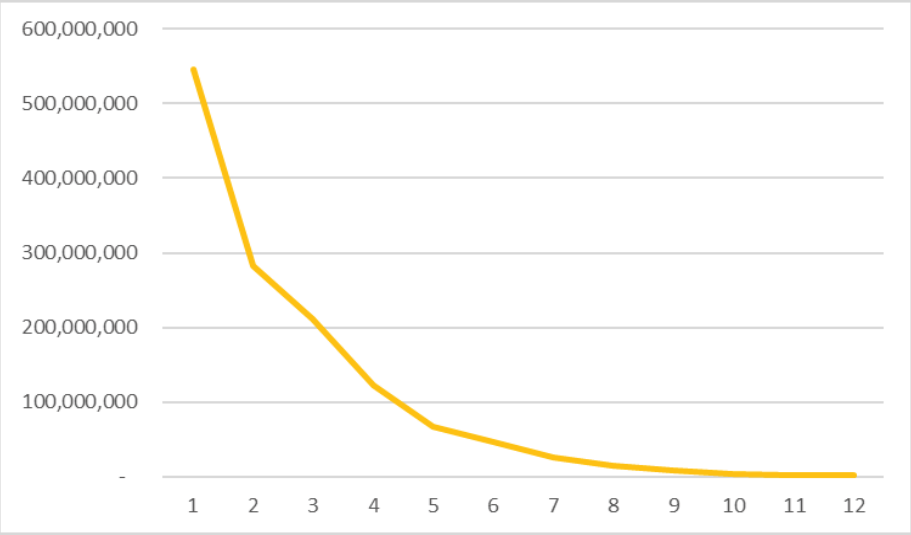
Methodology

The cost to payers and the share of those additional costs that accrues to voucher sellers (i.e. to HUMN originators) is calculated in the following way. First, a representative annual cohort of RDP-protected products is constructed based on IQVIA sales data. This will give the profile of the potential voucher buyers. From this can be inferred the cost of a given annual number of vouchers to public authorities, the share of this expenditure that will go to the intended recipient i.e. the voucher seller, and the cost to patients in the form of lower uptake.

The RDP-protected products with expiry over an 11-year period (2014-2024) were used to construct the representative cohort. First, the medicines are each assigned to their respective annual cohorts. Second, the medicines with expiry in the same year were ranked according to the value of EU sales in the top selling year for each medicine according to IQVIA data. The average peak sales value of the top product from each year group gives the peak year sales value of the top product in the representative sample. The average value of the second product from each year group gives the peak year sales value of the second product in the representative sample and so on.

Table 31 – Peak sales of products in the representative annual cohort

Product	Peak sales
1	545 000 000
2	282 654 545
3	210 890 909
4	122 727 273
5	66 854 997
6	46 362 340
7	25 833 879
8	14 449 938
9	9 270 111
10	3 555 616
11	2 021 996
12	1 807 804



A model based on the decline in revenue experienced by a representative RDP-protected product after protection expiry is used to calculate the cost and benefit to various stakeholders of a one-year exclusivity extension for such a product. Table 32 illustrates the calculation of the value of a

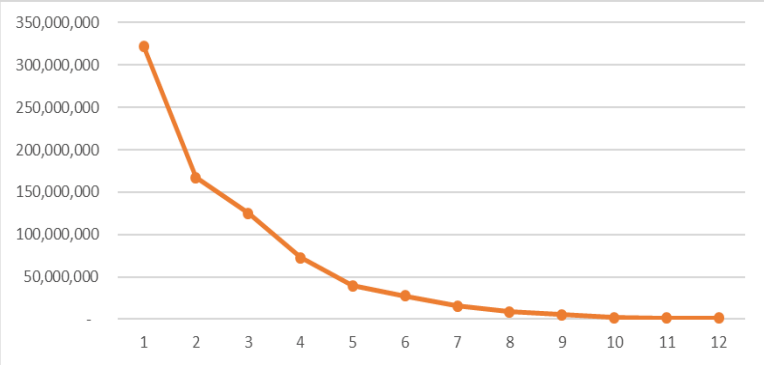
voucher to a voucher buyer, taking as an example the top selling product in the representative cohort.

Table 32 – impact of a voucher on stakeholders, expressed as a percentage of peak year sales of the medicine for which the voucher is bought

	Baseline	Voucher	Change	Change %
Originator sales	981	1063	82	8%
Generic sales	130	100	-30	-23%
Cost to public payer	1111	1163	52	4.7%
Cost of baseline volume	1111	1192	81	7.3%
Patients served	1445	1390	-55	-3.8%
Originator volume	1059	1111	52	
Originator distribution cost	212	222	10	
Net marginal revenue (NMR)	769	841	72	9%
Net present value of NMR			59	

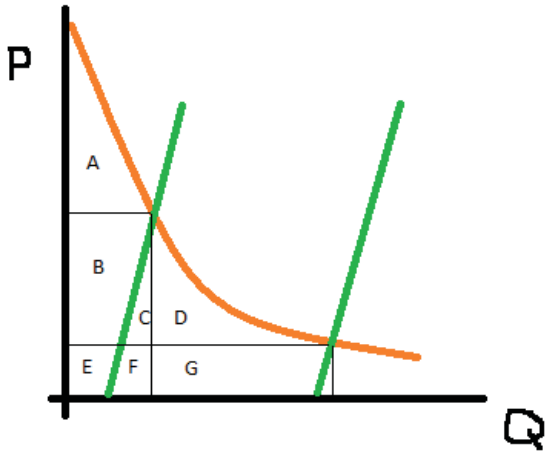
The change in net marginal revenue of the originator (i.e. the voucher buyer) gives the value of the voucher for each buyer and therefore the willingness to pay of each potential buyer. It is thus possible to construct a demand curve for the market for RDP extension vouchers.

Figure 15 – demand function for vouchers



Given this demand function, the supply curve (whose position depends on the HUMN criteria) will determine the equilibrium price.

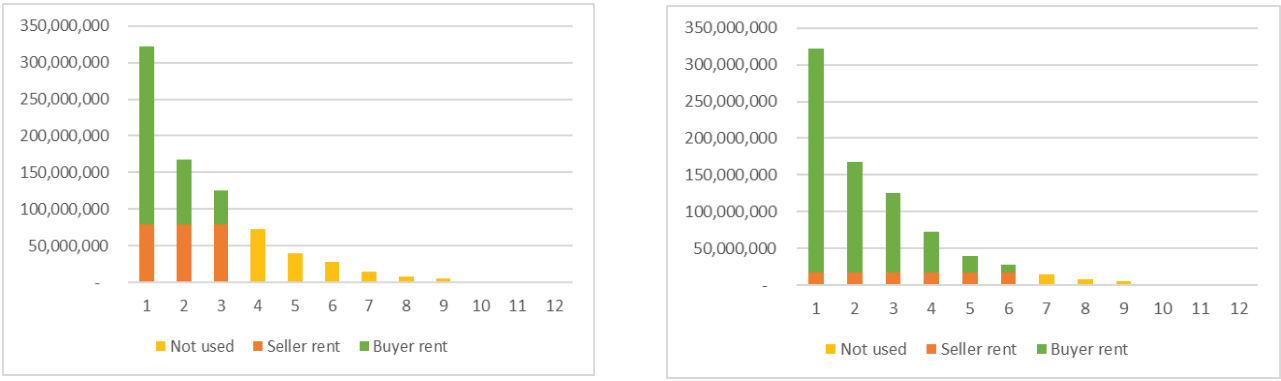
Figure 16 - equilibrium price for vouchers



The supply function can be represented as a vertical line or, arguably, as a steep upward sloping line reflecting the incentive impact of the scheme. Given the shape of the demand curve, the price drops sharply as the number of vouchers increases from one to three to five. In Figure 16 the rent represented by areas B and C go to the voucher seller with a smaller number of vouchers. With a larger number, B and C go to the buyer, along with D. The seller is left with only E, F and G.

In Figure 17 the analysis applied to the representative cohort. Thus, with one voucher issued, the seller's share of the voucher rent is 57%. With three, it is already less than the buyer's share at 39%. With six, it is only 13%, with the remaining 87% wasted on benefits accruing to companies that are not the intended beneficiaries of the scheme.

Figure 17 – The seller and buyer share of voucher rent varies with the number of vouchers



While the originator's revenue increases with a corresponding increase in the expenditure by payers, this is in part offset by a decrease in the revenues of generic manufacturers. However, the implied cost is also an understatement, given that fewer patients will be served over the period considered as a result of higher prices. The cost of the catering to the higher number of patients served in the baseline at the prices seen in the policy scenario is higher.

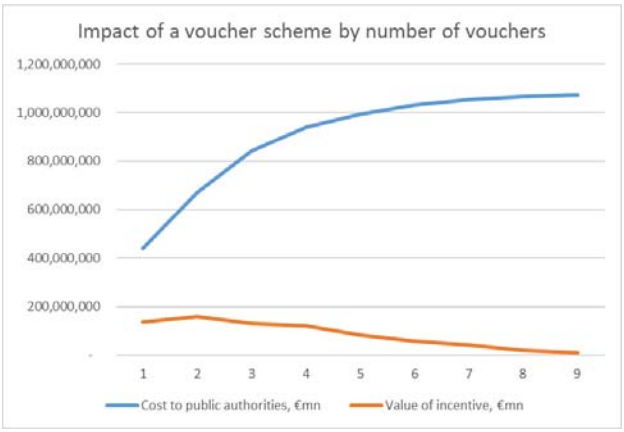
As explained above, there may be up to 6 HUMN medicines for rare diseases per year which would imply the use of six possible vouchers. The matrix below then gives a total annual combined cost to the public payer of **over a billion euros**.

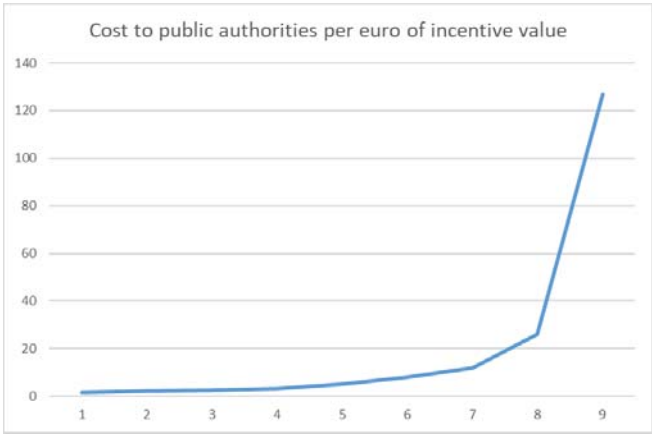
Table 33 – Number of vouchers and financial impact on health systems

# of vouchers	Peak sales	Cost of nth voucher to payers (81% of peak sales)	Cumulative cost to payers
1	545,000,000	441,450,000	441,450,000

2	282,654,545	228,950,182	670,400,182
3	210,890,909	170,821,636	841,221,818
4	122,727,273	99,409,091	940,630,909
5	66,854,997	54,152,548	994,783,457
6	46,362,340	37,553,495	1,032,336,952
7	25,833,879	20,925,442	1,053,262,394
8	14,449,938	11,704,450	1,064,966,844
9	9,270,111	7,508,790	1,072,475,634
10	3,555,616	2,880,049	1,075,355,682
11	2,021,996	1,637,817	1,076,993,499
12	1,807,804	1,464,321	1,078,457,821

Figure 18 – Cost to public authorities per euro of incentive value





A similar analysis has been set out in a paper that appeared in *Health Review* in 2016[227]. Some corroboration of this analysis can be seen from the US experience of issuing priority review vouchers for various classes of products. While a priority review voucher is a distinct mechanism, the effect of the number of vouchers would be similar, as more vouchers would mean that they would be used for less and less revenue-generating products. After what may have been a "teething phase" of the first two, the relationship between the number of vouchers and the price at which they are sold would appear to correspond to the above supply and demand based analysis.

Figure 19 - Number of PRV awarded by FDA

[227] The Commercial Market For Priority Review Vouchers | Health Affairs

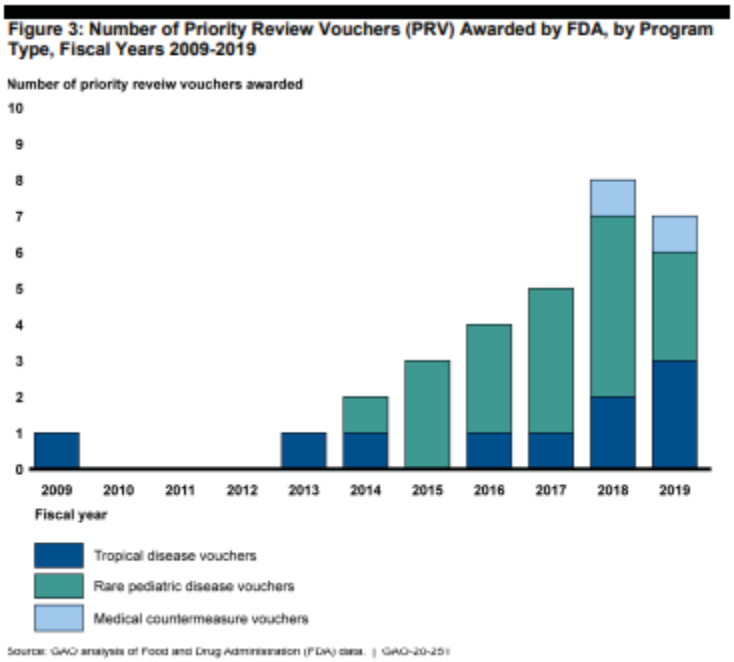
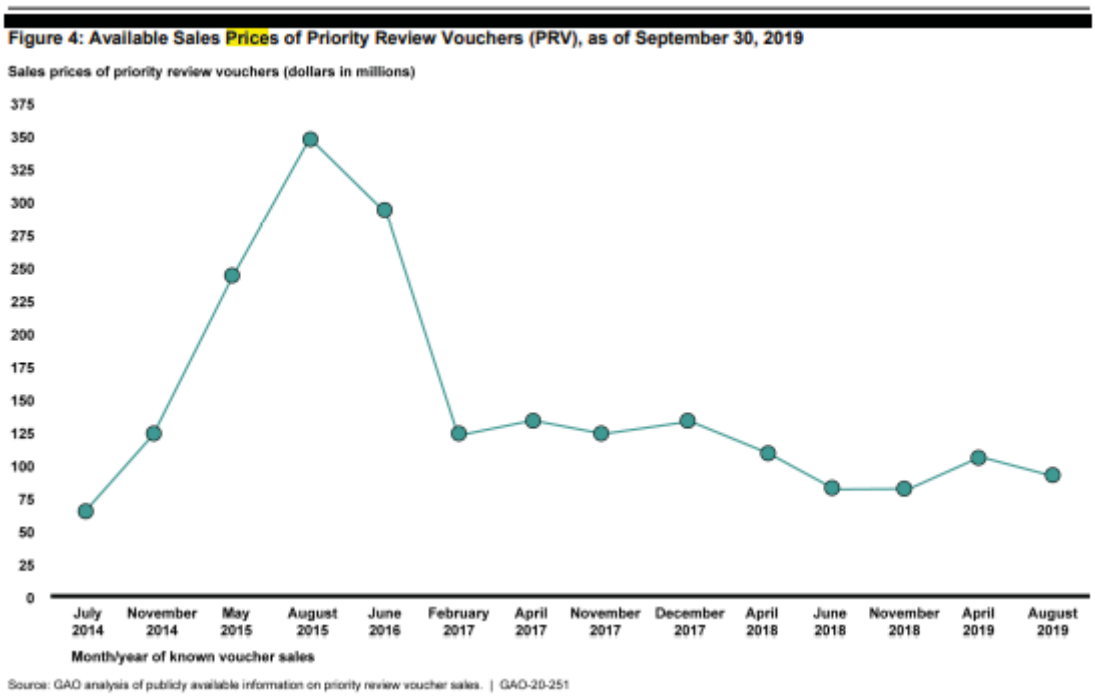


Figure 20: sales price PRV



6. *The impact of measures to improve market access*

The baseline takes account of the preferred option in the revision of the general pharmaceutical legislation, which makes the last year of RDP conditional on authorization in all Member States within two years. However, since orphan medicine originators will benefit from ten years of market exclusivity in the baseline, they will continue to enjoy ten years of protection from generic competition, even if they do not meet the condition. For this reason, Option C for the orphan

revision provides for a conditionality that matches the one that applies to RDP, so that the incentive extends to orphan products that rely on market exclusivity as their last line of protection. Option B, by eliminating market exclusivity has the same effect of allowing the incentive to apply to ME-reliant orphan medicines.

Table 34 - Regulatory protection and market exclusivity periods in different scenarios under Option A

Option A	Not launched in all EU		Launched in all EU		Access premium
	Regulatory protection	Market exclusivity	Regulatory protection	Market exclusivity	
Standard orphan medicines	8 years	**10 years**	9 years	**10 years**	0 year
HUMN orphan medicines	8 years	**10 years**	9 years	**10 years**	0 year

Table 35 - Regulatory protection and market exclusivity periods in different scenarios under Option B

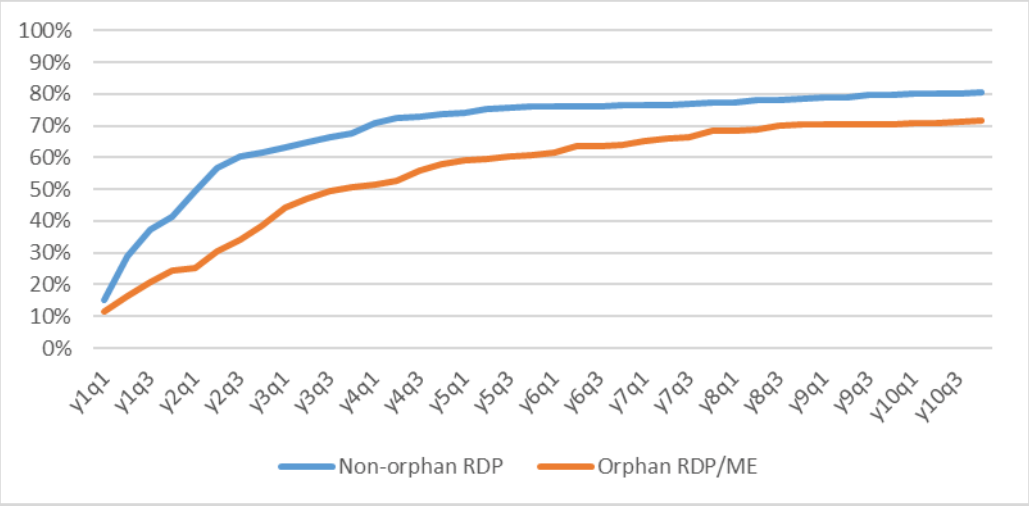
Option B	Not launched in all EU		Launched in all EU		Access premium
	Regulatory protection	Market exclusivity	Regulatory protection	Market exclusivity	
Standard orphan medicines	8 years	**0 years**	9 years	**0 years**	+1 year
HUMN orphan medicines	8 years	**0 years**	9 years	**0 years**	+1 year

Table 36 - Regulatory protection and market exclusivity periods in different scenarios under Option C

Option C	Not launched in all EU		Launched in all EU		Access premium
	Regulatory protection	Market exclusivity	Regulatory protection	Market exclusivity	
Standard orphan medicines	8 years	**8 years**	9 years	**9 years**	+1 year
HUMN orphan medicines	8 years	**10 years**	9 years	**11 years**	+1 year

IQVIA sales data was used to assess the baseline level of access to orphan medicines across 25 Member States[228] for orphan products in the relevant category (reliant on ME rather than SPC). For each molecule and each Member State, the first quarter in which meaningful[229] non-zero sales occurred for at least two successive quarters was taken to indicate the quarter in which the product reached that market. It was then possible to calculate for each products, how many Member States and what percentage of the EU population it had reached after a given number of quarters. Then, taking the average across all the products in the basket, we were able to plot the evolution of the average ME-dependent orphan product and compare it with that of the average RDP-dependent non-orphan product. To follow the evolution of market access over 10 years, the sample was restricted to only those products that are authorised between Q1 2010 and Q4 2011[230].

Figure 21 – Percentage of the EU population having access to the product overtime by protection type



The average ME-reliant orphan can be seen to fare considerably worse than the average RDP-reliant non-orphan. Not only is the final level of access lower, it is achieved more slowly. Deeper analysis point to higher coverage of products with higher sales and that larger member states with higher GDP tend to have a higher share of the products on their market.

Figure 22 – Percentage of population served over time

[228] NB. IQVIA MIDAS sales data were not available for Cyprus and Malta.
[229] At least 1% of the average EU per capita sales volume.
[230] The RDP-reliant non-orphan products in the basket were ABIRATERONE ACETATE, ACETYLSALICYLIC ACID!CLOPIDOGREL, AMLODIPINE!HYDROCHLOROTHIAZIDE!OLMESARTAN MEDOXOMIL, AMLODIPINE!TELMISARTAN, ASENAPINE, BROMFENAC, C1 INHIBITOR (HUMAN), CABAZITAXEL, CLEVIDIPINE, CORIFOLLITROPIN ALFA, DEXAMETHASONE, DEXMEDETOMIDINE, DUTASTERIDE!TAMSULOSIN, GIMERACIL!OTERACIL!TEGAFUR, METFORMIN!SAXAGLIPTIN, PITAVASTATIN, ROFLUMILAST, SILODOSIN, TAPENTADOL, THIOTEPA, VELAGLUCERASE ALFA
The ME-reliant orphan products were ANAGRELIDE, CLOFARABINE, DECITABINE, DEFIBROTIDE, ICATIBANT, MECASERMIN, MIFAMURTIDE, NELARABINE, STIRIPENTOL, TEDUGLUTIDE, THIOTEPA, VELAGLUCERASE ALFA, KETOCONAZOLE, MERCAPTOPURINE

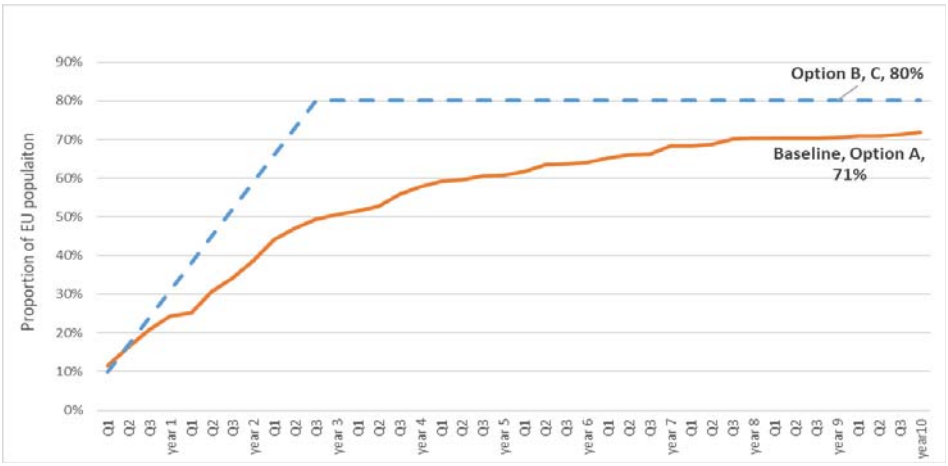


Figure 22 demonstrates the expected impacts of the various policy options on patient access[231]. Option B and C reach a higher plateau of 80% EU population covered, and also much faster than Option A/baseline, two years following authorisation. The maximum achievable access is less than for non-orphan medicines, given the sometimes extremely low or non-existent patient population in Member States. We based our estimation on data from SPC protected orphan medicines, which can reach an average 80% population coverage even in rare conditions, but with higher financial incentives. We assume, that soon after 2 years from authorisation this plateau would be reached, because of the incentive.

7. Medicines for children - Modelling changes in SPC-extension duration

a. Protection types and length in a sample of medicines

In the basket of products from IQVIA database with protection expiry between 2016 and 24, 20% of medicines (40/199) are benefiting either from the +6 months SPC extension (36) or from the two years market exclusivity extension (4) as last protection to expire. These products are highlighted in Figure 6, presented by the length of their overall protection. Importantly, those medicines that are protected by a patent or regulatory protection as a last line of protection (90/199) and not by SPC or market exclusivity, cannot benefit from the reward for carrying out studies in children.

It is important to note that from the IQVIA database it is not possible to determine which products have been studied in children. On the basis of historical data it can be assumed that around 50% of the products under development are granted a full waiver from the obligation of conducting a PIP. By extrapolation, it can be expected that also in the basket considered only 100 of products were subject to the obligation to conduct a PIP. Which brings the percentage of products rewarded with a PIP extension to around 40% of the eligible products.

As explained in the previous section, the number of SPC extensions are smaller than we would expect from the number of new medicines authorised with a PIP obligation, due to a lag in completing PIPs, often many years after authorisation of the adult medicine. Interestingly, medicines with high sales are good at timely completion of the PIPs, we have noted that out of 12 blockbuster medicines (those that have a revenue of €1 billion per year in the EU market) in our basket, 8 had a paediatric extension. In their case, the motivation was high: a 6-month extension generates hundreds

[231] It is hereby important to keep in mind that these incentives work with medicines that are not protected by SPC or patents, as those IP incentives provide longer protection than the maximum achievable market exclusivity for more than half of all newly authorised medicines.

of millions of additional protected revenues. This is reflected in Table 4, those medicines for which the SPC extension is the last layer of protection have longer protection times, and higher average revenues than all the other medicines.

Figure 23 - Distribution of products with paediatric extension by length of protection

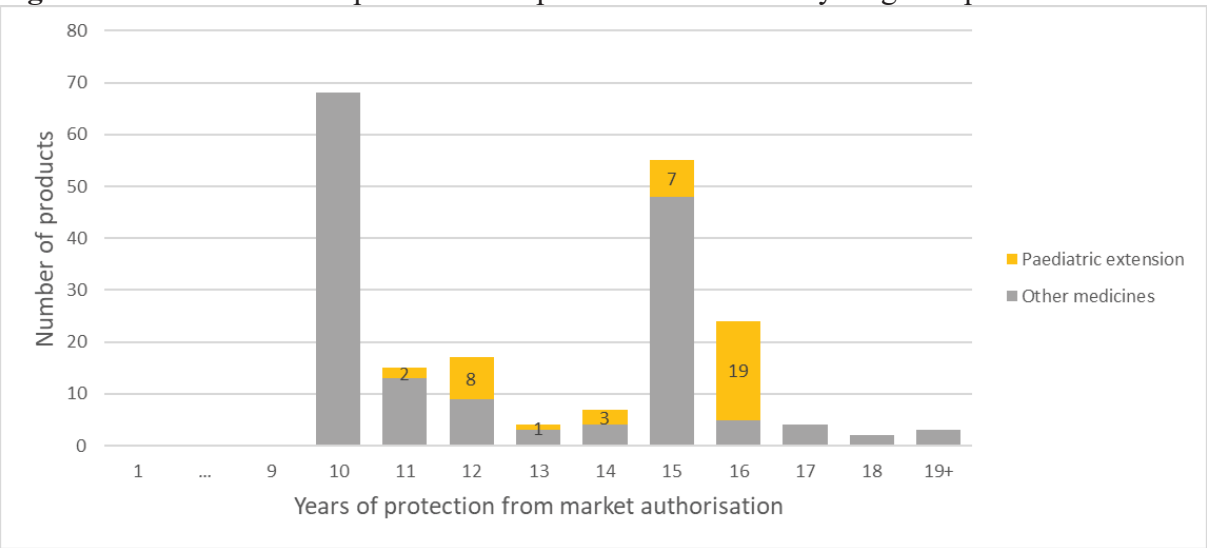


Table 37 - Peak annual sales and protection period of products with paediatric extension

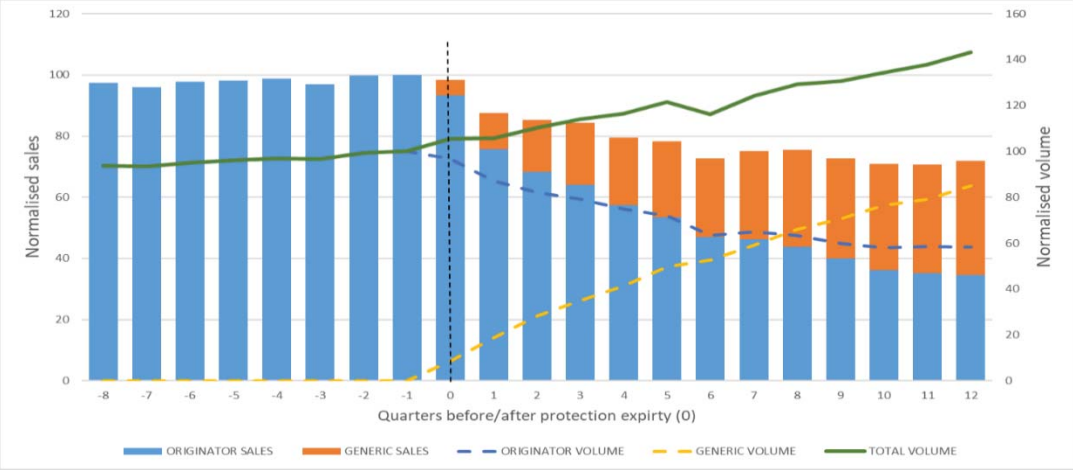
	Avg. peak annual sales	Avg proection period
Paediatric extension	€ 540.6 m	14.3 years
Other medicines	€ 199.5 m	12.7 years

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

To measure the impacts of changes in the SPC extension, we used the same concept as for the general pharma and for the orphan medicines. However, those medicines benefiting from the SPC extension have typically longer protection and generate much higher revenues than the RP protected ones, which serve the basis of the general pharma analogue. The high sales medicines are more prone to generic competition, because of the lucrative market, the generic competitors come faster, in bigger number and with more aggressive price competition.

To properly account for this difference, we built a new analogue based on a different basket of products is used. For this exercise, we considered the 11 products[232] whose SPC protection expired in France, Germany, Italy and Spain between 2016 and 2018 and for which SPC protection is the last line of protection. Since the options concern increases or decreases in protection by six months, quarterly rather than annual data were used.

[232] ADALIMUMAB, BOSENTAN, CASPOFUNGIN, ENTECAVIR, EZETIMIBE, IMATINIB, IVABRADINE, RUPATADINE, TIGECYCLINE, TIOTROPIUM BROMIDE, VORICONAZOLE



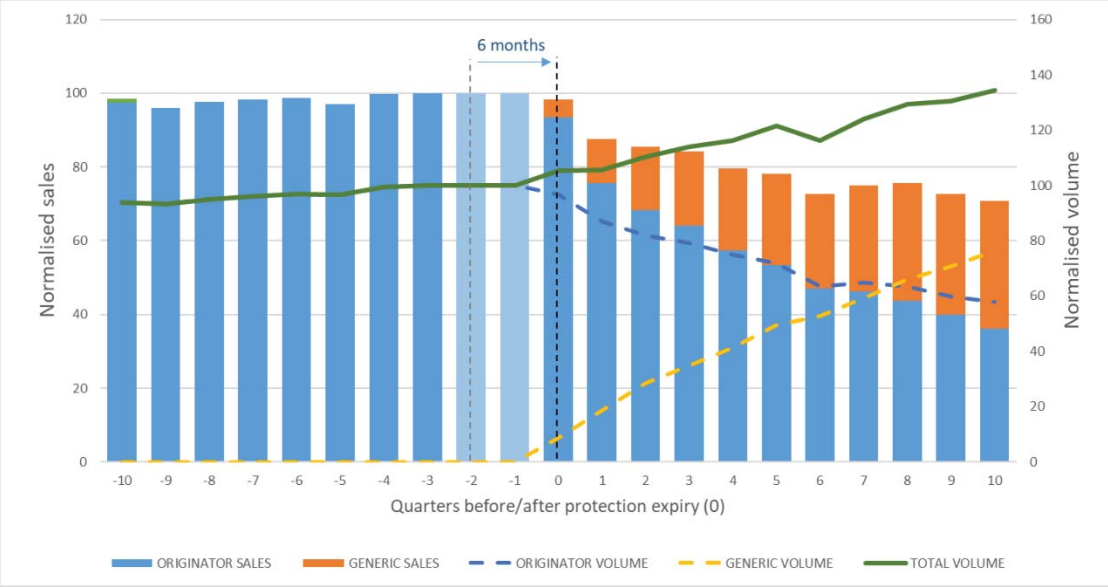
quarter from expiry		-8	-4	-1	0	4	8	12
ORIGINATOR	SALES	97	99	100	93	57	44	35
GENERIC	SALES	0	0	0	5	22	32	37
TOTAL	SALES	97	99	100	98	80	76	72
ORIGINATOR	VOLUME	94	97	100	97	75	63	58
GENERIC	VOLUME	0	0	0	9	41	66	85
TOTAL	VOLUME	94	97	100	105	116	129	143
ORIGINATOR	PRICE	1.04	1.02	1.00	0.97	0.77	0.69	0.59
GENERIC	PRICE				0.56	0.53	0.48	0.44
TOTAL	PRICE	1.04	1.02	1.00	0.93	0.68	0.58	0.50

The analogue indeed confirmed, that for a typical beneficiary of the SPC extension changes from generic entry are more dramatic. 3 years after the expiry, the volume of generic and originator medicines combined has increased by 43% (suggesting 43% more patients being able to benefit from the medicine) and average price halved, compared to quarter -1, the last protected quarter. As in the general pharma, we have modelled changes by moving the expiry point 2 quarters back or ahead within our 21-quarter long observation period.

c. Modelling the economic impact of increasing SPC extension

We use the same data as presented above and assume that after the Q-1 there will be an additional 2 quarters of peak sales protected by a 6-month additional SPC extension. We will use the result of this model to estimate the proportionate effect of the 12-month SPC extension incentive for UMN addressing medicines in Option A. We assume that pre-expiry sales trajectory is unchanged, the market dynamics of generic competition post expiry is unchanged. In the figure below thus data associated with a new Q-1 is added twice and the baseline Q11 and 12 are removed to maintain the overall observation period of 21 quarters. Figure X

Figure 24 - Normalised volume and sales data for products with +2 quarters of SPC extension



	Baseline	12-month SPC ext	change
Originator protected sales	785	985	**+200**
Originator contested sales	695	625	**-70**
Originator gross profit	975	1101	**+125**
Generic sales	327	254	**-73**
Generic gross profit	108	84	**-24**
Cost to public payer	1807	1865	**+58**
Volume (patients served)	2360	2278	**-81**
Cost of baseline volume	1807	1923	116

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

Using the above model for the product lifetime, we can make the following observations at product level:

- Originator companies increase pre-expiry sales due to additional 6 months of monopoly sales by 200 (normalised units). In terms of gross profit, this is 125 more normalised unit.
- Generic companies' start to benefit from sales 2 quarters later, and thus generic sales are reduced by 73 (normalised units), and gross profit is reduced by 24 (normalised unit) compared to the baseline.
- Healthcare payers pay more overall due to an increase in the average price they need to pay for a standard unit of the product. The total cost for healthcare payers is thus +58 (normalised units) over the product lifetime compared to baseline
- Patients lose -81 (normalised units) in decreased volumes of the medicine over the lifetime of the product compared to baseline.

i. Monetising the systemic effects of 12-month SPC extension for medicines addressing UMN (Option A)

We expect that 20% of the new products will meet the UMN criteria, therefore out of the expected yearly 10 SPC extension, 2 would be for UMN addressing medicine. Increasing the current 6-month

SPC extension to 12 for these medicines would result in the following impacts, by using the changes values of the models and the value of €540 m peak annual sales, derived from historic data.

Table 38 - Impact of 6 months protection increase (+12 months SPC extension) for UMN on different stakeholders

	avg product (€540 m annual sales)	Systemic impact (2 extensions/year)
Originator gross profit	**+€169 m**	**+€338 m**
Generic gross profit	-€32 m	-€64 m
Public payer's gain/loss (cash)	-€78 m	-€156 m
Δ of patients treated (monetised)	-€78 m	-€156 m
Patient and payer gain/loss	**-€156 m**	**-€312 m**

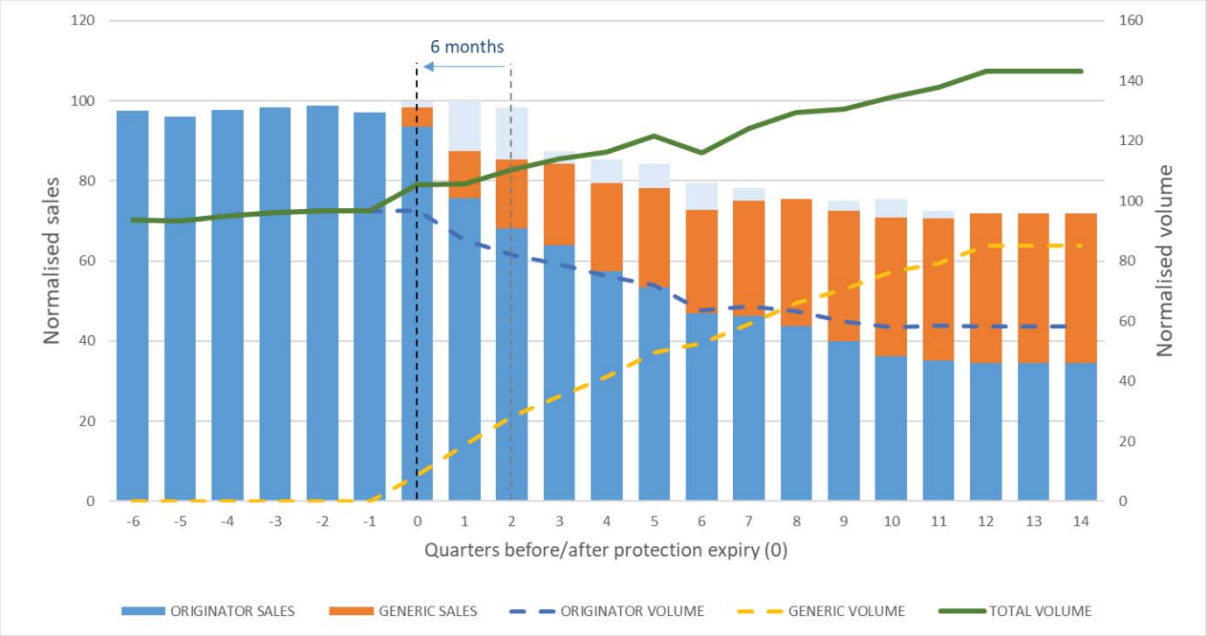
Thus, benefiting originator companies would increase profits by €338 m at a cost of €312 m to the public. Generic companies would experience a €64 m decrease in their gross profits.

d. Modelling the economic impact of decreasing SPC extension

Option B would abolish SPC extension reward, thus reducing protection by 6 months compared to the baseline. This will be the new scenario for the analogue. In the model, we assume that after 3 full years of generic competition an equilibrium value of annual sales and volume of product sold are established and thus we can use Q12 data for originator and generic products as long-term level to calculate the value of ME loss over the product lifetime.

We also assume that the pre-expiry sales trajectory is not changed by company behaviour and thus the baseline Q-1 and Q-2 sales are lost under the new regime. In the figure below thus the original Q-1 and Q-2 values are removed and Q13 and Q14 values are added at equilibrium level. In addition, we assume that the market dynamics of generic competition (between Q0 and Q12) in the new regime will not change compared with the baseline 6-month SPC extension.

Figure 25 - Normalised volume and sales data for products with -2 quarters of SPC extension



	Baseline	No SPC	change
Originator protected sales	785	585	**-200**
Originator contested sales	695	764	**+69**
Originator gross profit	975	850	**-125**
Generic sales	327	402	**+75**
Generic gross profit	108	133	**+25**
Cost to public payer	1807	1751	**-56**
Volume (patients served)	2360	2447	**+87**
Cost of baseline volume	1807	1695	-112

Using the above model we can make the following observations at product level:

- Originator companies' pre-expiry sales loss of -200 (normalised units) translates to a decrease in originator's gross profit of -125 (normalised units) over the observed 21-quarter period.

  We know that pharmaceutical industry is one of the most R&D intensive sector and they reinvest a large share of their revenue into innovation for new products and technologies. This share is 20% on average globally[233] and we can assume that the revenue loss will translate to a loss of innovation budget.

- Generic companies' start to benefit from sales half year earlier compared to baseline, and thus reach equilibrium level 2 quarters earlier. These two extra quarters of equilibrium generic sales of +75 (normalised units) are equal to +25 (normalised units) gross profit gains.
- Healthcare payers pay less overall due to a decrease in the average price they need to pay for a standard unit of the product. In the baseline +6 months SPC extension regime, the total lifetime

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

sales is 1807 (normalised units) and in the new 8-year protection regime the same volume at the new prices would be 1756 (normalised units). Thus in the new situation healthcare payers would pay 56 (normalised units) less.

In the real situation, however, healthcare payers may not realise this nominal saving but choose to purchase more units of the medicine at a lower price for the healthcare system and expand coverage of patients. The difference in the cost of the baseline volume (at new prices) contains both the decreased payment and the extra volumes, so the joint gain for the public is 112 (normalised unit).

- Patients benefit due to the increased volume of the medicine sold after protection expiry (6 months earlier) which then reach more patients creating higher level of health benefits. In the model, the total volume increases as soon as generic products enter the market and volume of generic products surpasses that of the originator product by year 4 after generic entry. In the new regime the total volume sold increases by +87 (normalised units).

i. Monetising the systemic effects of abolishing SPC extension (Option B)

Under option B, medicines which would currently be eligible for the 6-months SPC extension will lose such protection. Generic medicines could enter the market earlier and public authorities would pay less, for more patients served. We have adjusted our model to the new expiry and compared it to the baseline. Table 38 shows the impact of the change for all stakeholders, both at an individual product level, and at systemic level for all 10 products, that would benefit from the extension in the baseline.

Table 39 - Impact of 6 months protection reduction on different stakeholders

	avg product (€540 m annual sales)	Systemic impact (10 extensions/year)
Originator gross profit	**-€169 m**	**-€1,690 m**
Generic gross profit	+€33 m	+€330 m
Public payer's gain/loss	+€76 m	+€760 m
Δ of patients treated (monetised)	+€75 m	+€750 m
Patient and payer gain/loss	**+€151 m**	**+€1,510 m**

At an individual product level, the reduction is a significant loss to the **originator company**, an average SPC extended product would lose -€169 m gross profit. The **generic** products would have +€33 m higher profits thanks to the earlier entry. The **public payer** would experience +€76 m yearly savings, however this is not the only benefit for the public. Not only the total cost would be less, but more **patients** could be served with the more affordable medicine, adding an additional +€75 m monetised patient benefit. Overall the public gains €151 m thanks to the reduction. Looking at systemic level, the loss of 10 SPC extensions compared to the baseline would cause €1.690 m profit loss to the innovator industry annually. On the other hand, the public would make significant savings, to the tune of €1,510 m per year.

e. Cost of a PIP

Building on data reported in the Joint Evaluation Table 7, which provides the probability that each cost is incurred during the conduction of a PIP, it has been estimated the average administrative (0.5 M€) and R&D (22.2 M€) costs of a completed PIP.

TABLE 40 - Estimated costs of a PIP

Estimated costs of a PIP broken down to stages	*est. avg cost of a PIP stage (EURO)*	*Estimated to happen in PIPs*	*est. avg cost of a completed PIP (EURO)*
Preparation of the initial PIP application	400,000	100%	400,000
Annual reporting and further PIP modifications	100,000	55%	55,000
Other administrative costs	200,000	42%	84,000
estimated AVG administrative cost per completed PIP			**539,000**
In vitro studies and animal studies	800,000	40%	320,000
Development of a paediatric formulation	1,600,000	47%	752,000
Phase II paediatric clinical trials	7,300,000	48%	3,504,000
Phase III paediatric clinical trials	15,700,000	72%	11,304,000
Other R&D costs	14,400,000	44%	6,336,000
estimated AVG R&D cost per completed PIP			**22,216,000**

Source: calculation on data collected from the Joint Evaluation

To estimate the total administrative costs incurred yearly by industries, we have multiplied the number of PIPs completed per year with the estimated AVG administrative cost per completed PIP (539 k€).

The completion of a PIP requires time, the analysis – conducted on 205 pMPs with a PIPs agreed during 2007-2020 – of the time needed to obtain a market authorisation (MA) for the paediatric indication after the completion of the PIP, identified an average time of 5.3 years – rounded to 5 - from the first EMA opinion to the MA date[234] (information on both dates are available for 119 of the 205 pMPs, 58%), in line with the 7 years of the "average planned duration of a PIP, from the date of initial application to the planned completion date" reported in the Joint Evaluation. Therefore, it was assumed that R&D costs of a PIP (22.2 M€) are equally distributed over the 5-year period preceding the MA (year of obtainment included) to estimate the total R&D costs incurred yearly by industries

ANNEX 5: HOW OPTIONS ARE EXPECTED TO CONTRIBUTE TO THE ACHIEVEMENT OF THE OBJECTIVES

1. Options for rare diseases

Objective	Common elements	PO A	PO B	PO C[235]

[234] It has been observed that "*The median time to the composite endpoint of first results reporting (either in a trial registry or peer-reviewed journal) was 4.7 years (IQR 3.2 to 5.8 years) from the date of publication of the PIP*" [Hwang, T. J., Tomasi, P. A., & Bourgeois, F. T. (2018). Delays in completion and results reporting of clinical trials under the Paediatric Regulation in the European Union: A cohort study. PLoS medicine, 15(3), e1002520. https://doi.org/10.1371/journal.pmed.1002520].

[235] All the options (PO A, PO B and PO C) include also common elements. Common elements are presented separately only once to facilitate presentation and avoid repetitions.

1. Foster innovation and investment in research and development of medicines for rare diseases and for children especially in areas of (high) unmet medical need	Criteria to identify products addressing HUMN will be set in the Orphan Regulation. Products addressing HUMN will be entitled to increased scientific support by the Agency. *These measures are expected to facilitate the development and faster development of products addressing HUMN*	10 years of market exclusivity (ME) + transferable regulatory protection voucher for HUMN products *The 10–year market exclusivity (the same for all orphan products categories) will foster the development of research into orphans in general, hence contributing to innovation. It is the transferrable regulatory protection voucher (granted to products addressing HUMN) which is expected to foster research into HUMN (and hence also more targeted innovation)*		Variable duration of the ME: 10 years of ME for HUMN products; 9 years of ME for new active substances; 5 years of ME for well-established use products. *While the market exclusivity targets all orphan products, a modulated duration of ME will better direct research into HUMN and into new active substances.*
2. Create a more balanced and competitive system that keeps medicines affordable for health systems and patients while rewarding innovation	Generics/biosimilars can enter the market at day-1 of the expiry of the exclusivity period by allowing the filing of an application prior to expiry. *This measures aims at a faster entry of cheaper generics (affordability), which at the moment is delayed by the time needed from filing of the application until granting an authorisation (120 days). At the same time, the measure does not impact innovation, as the ME period remains intact.* Reduction of consecutive periods of market exclusivity for new indications of the same orphan medicine by introducing them under the same "Global Marketing Authorisation" (GMA). *This measure, by proving the extension of ME for only two first new indications, will allow (cheaper) generics to enter*		No ME *No ME exclusivity will ease the entry of generics, but at the same time, it may be questioned whether innovation will be sufficiently rewarded.*	Variable duration of the ME *This measure will create a more balanced system where especially innovation and addressing HUMN is rewarded. Authorisation of orphan products with well-established use will still be rewarded (as it is important to have products officially authorised for a specific use on the market), but with a shorter 5-year ME. Variable duration of ME will help faster entry of generics (to address affordability).*

	faster the market (affordability). At the same time, it creates a better balance between the need to reward innovation (while avoiding unjustified benefitting from the system|) and the need for a fast generics entry, The market exclusivity granted to a second generation product that is similar to the first generation product shall not be applied in respect of generic products of the first reference product for which the market exclusivity expired. *As above, this measure preserves innovation and blocks the unjustified benefiting from the system of incentives ('evergreening'), while allowing a faster entry of generics (affordability).*			
3. Enable timely patient access to orphan and paediatric medicines in all Member States	Generics/biosimilars can enter the market at day-1 of the expiry of the exclusivity period by allowing the filing of an application prior to expiry. *This measure ensures timely access of generics. See also explanations for this measure in point 2.* Reduction of consecutive periods of market exclusivity for new indications of the same orphan medicine by introducing them under the same "Global Marketing Authorisation" (GMA). *This measure*			Extension of the ME if market launch in all EU Member States (for HUMN products and new active substances). *This measure awards those companies which made efforts to reach out to all MS, even those where marketing products is less attractive for companies (due to limited public funds to buy expensive medicines, small markets, etc.)*

	ensures timely access generics. See also explanations for this measure in point 2. . The market exclusivity granted to a second generation product that is similar to the first generation product shall not be applied in respect of generic products of the first reference product for which the market exclusivity expired. *This measure ensures timely access generics. See also explanations for this measure in point 2.* Encourage companies that lose the commercial interest in an orphan medicine to offer it for transfer to another company rather than withdrawing it *This measure will help patients' access to a medicine which risks withdrawal from the market.* The duration of the orphan designation (assigned early in the development of a product and prior to obtaining a marketing authorisation) will be capped for newly designated orphan medicinal products at 7 years. *This measure is expected to motivate the sponsor to timely develop the product and as a result it helps timely patients' access.*			
4. Reduce the regulatory burden and provide a flexible regulatory framework.	Provide for the possibility to adapt the current definition of an orphan condition *This measure opens up the possibility that the current*			

	definition of an orphan condition may be easier adapted (for example to scientific developments). The orphan designation criterion on the basis of return on investment will be deleted. *This measure 'cleans up' a criterion to get an orphan designation that has become obsolete.* Responsibility for adopting decisions on 'orphan designations' will be transferred from the Commission to the Agency. *This measure will facilitate and expedite the procedure, as the same body (Agency) will be responsible for a scientific opinion and for an orphan designation (while currently the Commission gives the decision on an orphan designation).*			

Further explanation of important parts of the common elements:

- ***Global marketing authorisation*** (*Reduction of consecutive periods of market exclusivity for new indications of the same orphan medicine by introducing them under the same "Global Marketing Authorisation" (GMA).*

'Global marketing authorisation' is a concept which exists already under Directive 2001/83/EC (Article 6(1)) and means that a medicinal product has been granted a marketing authorisation, any additional strengths, pharmaceutical forms, administration routes, presentations, as well as any variations and extensions shall also be granted an authorisation in accordance with the first subparagraph or be included in the initial marketing authorisation. All these marketing authorisations shall be considered as belonging to the same global marketing authorisation. A measure proposed in this IA under the Orphan Regulation uses the same concept, but for the purpose of indications as one medicinal product may have a several indications (an indication means a medical condition that a medicine is used for. This can include the treatment, prevention and

diagnosis of a disease[236]). An indication should clearly state the disease/condition and population that a medicine is intended to treat. What is taken into account is severity of the disease, the place in the therapy, e.g. 1st, 2nd line, use in the combination therapy and other[237]. As these indications may be formulated narrowly, the measure of reduction of ME, which would be granted only for two indications, prevents drawing unjustified benefit from the ME.

- ***Transfer of the orphan marketing authorisation*** (*Encourage companies that lose the commercial interest in an orphan medicine to offer it for transfer to another company rather than withdrawing it*)

At the moment companies which lose the commercial interest in an orphan medicine may withdraw it from the market with no regulatory consequences, while generic products will not necessarily be interested to fill in the gap, either (rare diseases are characterised by very small patient populations). Even if another company would be willing to take over, the fact of withdrawal may be not sufficiently publicised and other forms of encouragement not provided.

- ***Duration of orphan designation*** (*The duration of the orphan designation (assigned early in the development of a product and prior to obtaining a marketing authorisation) will be capped for newly designated orphan medicinal products at 7 years)*

Currently, the orphan designation once granted is not limited in time. There may be situations where the orphan designation is lost (see Article 5 (12) of the Orphan Regulation)[238], but the lapse of time is not one of them. Several orphan designations may be introduced to the Register of Orphan Medicinal Products for the same condition, all of them entitled to pre-authorisation scientific and procedural facilitations, so one designation does not block research on other products. However, as the ultimate purpose is to deliver the product to the patient, companies should be encouraged to swiftly proceed to the marketing authorisation stage. The overpopulation of the Register with 'old' designations is also not good for its readability. As the average time the average time between orphan designation and MA Application (MAA) is 5 years, a somehow longer period of seven years, was suggested for a cap.

- ***Designation procedure*** (*Responsibility for adopting decisions on 'orphan designations' will be transferred from the Commission to the Agency.)*

The procedure for designation is set out in Article 5 of the Orphan Regulation. The applications for orphan designation are examined by the EMA's Committee for Orphan Medicinal Products (COMP), using the network of experts that the Committee has built up. The evaluation process takes a maximum of 90 days from validation. The Agency sends the COMP opinion to the European Commission, which is responsible for adopting a decision on the orphan designation within 30 days of receipt of the opinion. The full list of orphan designations is available in the Community register of orphan medicinal products for human use, managed by the Commission. In the proposed change, the responsibility for adopting decisions would be transferred to the Agency, which is expected not make the procedure faster and less burdensome.

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[236] Indication | European Medicines Agency (europa.eu)
[237] Wording of therapeutic indication - guide for assessors (europa.eu)
[238] (a) at the request of the sponsor; (b) if it is established before the market authorisation is granted that the criteria laid down in Article 3 are no longer met in respect of the medicinal product concerned; (c) at the end of the period of market exclusivity as laid down in Article 8.

2. Options for medicines for children

Objective	Elements common to all PO	PO A (SPC extension and novel incentives for UMN products)	PO B (No SPC extension)	PO C[239] (6 months SPC extension)
1. Foster innovation and investment in research and development of medicines for rare diseases and for children especially in areas of unmet need.	Criteria to identify products which have the potential to address unmet medical need of children will be defined in the general pharmaceutical legislation. Products which respond to these criteria will be entitled to increased scientific support by the Agency in the early phases of development this will help the development of novel products for children in areas of UMN. This measure is expected to benefit in particular SME who have more limited resources than big pharma companies Review of the waiver system to take into account the mechanism of action of a product: For products which, on the basis of scientific evidence on the mechanism of action, could also be effective against a different disease in children, clinical studies in children will have to be conducted. This will results in novel products for children in particular in areas in areas of UMN The new procedural system will allow for evolutionary PIP, which will help accommodate innovation	Novel incentives for UMN products. alternatively: A regulatory protection voucher (duration 1 year) or an extra 12 extra months SPC extension (on top pf 6 months' extension for all medicinal products) The novel incentives are expected to support the development of novel products for children in the areas of UMN		
2. Create a more balanced and competitive system that keeps medicines affordable for health	Abolishing the market exclusivity extension for completing PIPs would regulate a system that is not functioning well and		The abolition of the SPC extension will allow earlier generic entry and consequently	

[239] All the options (POA, POB and POC) include also common elements. Common elements are presented separately only to facilitate presentation and avoid repetitions.

systems and patients while rewarding innovation ;	will allow predictability for generic products and faster entry of generics in cases where products are not orphan medicines (which in turn will affordability due to lower prices of generics)		improve affordability for the health systems	
3. Enable timely patient access to orphan and paediatric medicines in all Member States;	Cap the duration of the deferrals to 5 years allowing faster development of medicines for children and consequently a higher access to them. The procedure for setting out a PIP will be streamlined and simplified allowing for quicker completion of the PIP and faster authorisation allowing a faster access to new medicines for children Abolishing the market exclusivity extension for completing PIPs would regulate a system that is not functioning well and will allow predictability for generic products and faster entry of generics in cases where products are not orphan medicines		No SPC extension will ensure a faster access to generic product	
4. Reduce the regulatory burden and provide a flexible regulatory framework.	Introduction of an evolutionary PIP model for specific paediatric developments Introduction of an simplified PIP model for specific paediatric developments) These measures are expected in resulting in reduced administrative costs for companies.			

Common elements:

- *Evolutionary PIP*

In the current legislation a complete development plan needs to be submitted to the Agency and agreed with at very early stage of development (after the completion of the pharmacokinetic and pharmacodynamics studies). For certain type of development this is problematic. For example when a molecules have never been used before, the detailed design of the each step of clinical development depends from the results obtained in the previous studies. The obligation to submit a full development plan at early stages obliges developers to make assumptions on the results that will be obtained in the future and results in subsequent need to modify the development plan (PIP) several times. This create delays in the completion of the PIP and administrative burden for the applicants and for the Agency.

With the concept of evolutionary PIP, certain type of developments, like molecules used for the first type in human, will be given the possibility to present a high level clinical development plan. The Agency will agree that the development plan will be completed and new information submitted and agreed at precise development steps. This will reduce the administrative burden and create when necessary a more agile PIP system.

- *Simplified PIP*

The PIP system has been put in place taking into account the development of products for adults for which a clinical development in children derives from the obligation imposed by the legislation.

However, there are cases, like paediatric only products or PUMA products which are developed specifically for children and would therefore be developed indipendedly from the paediatric Regulation. For these products the binding elements and the details that have to be presented in a PIP can be lowered. Specific guidelines on the elements that will be requested for this category of products will be determined by the Agency in close collaboration with interested stakeholders and the Commission.

- *Changes to the waiver system to take into account the mechanism of action of a product*

Currently, the obligation to conduct a PIP in children is waived in certain situation, for example when an adult product is intended for a disease not existing in children.

However, in certain cases the molecule in question, due to its molecular mechanism of action may be efficacious against a disease in children different from the one for which it was initially designed for use by adults. For example a product developed to treat an adult cancer, non-existing in children, could also be effective to treat a different type of cancer in children.

The waiver system is intended to be amended in order to oblige the conduct of PIP also when on the basis of the molecule of action of the product, it may treat a different disease in children.

A similar system has recently been introduced in the US[240].

- *Cap to the length of deferrals*

While the paediatric legislation foresees that clinical studies in children should be completed before the marketing authorisation in adult is granted, there is the possibility *to defer* the completion of some PIP studies only after the marketing authorisation of an adult product. It is envisaged to cap the maximum length of this derogation to 5 years, so that products reach children quicker than today.

- *Abolish the paediatric market exclusivity extension*

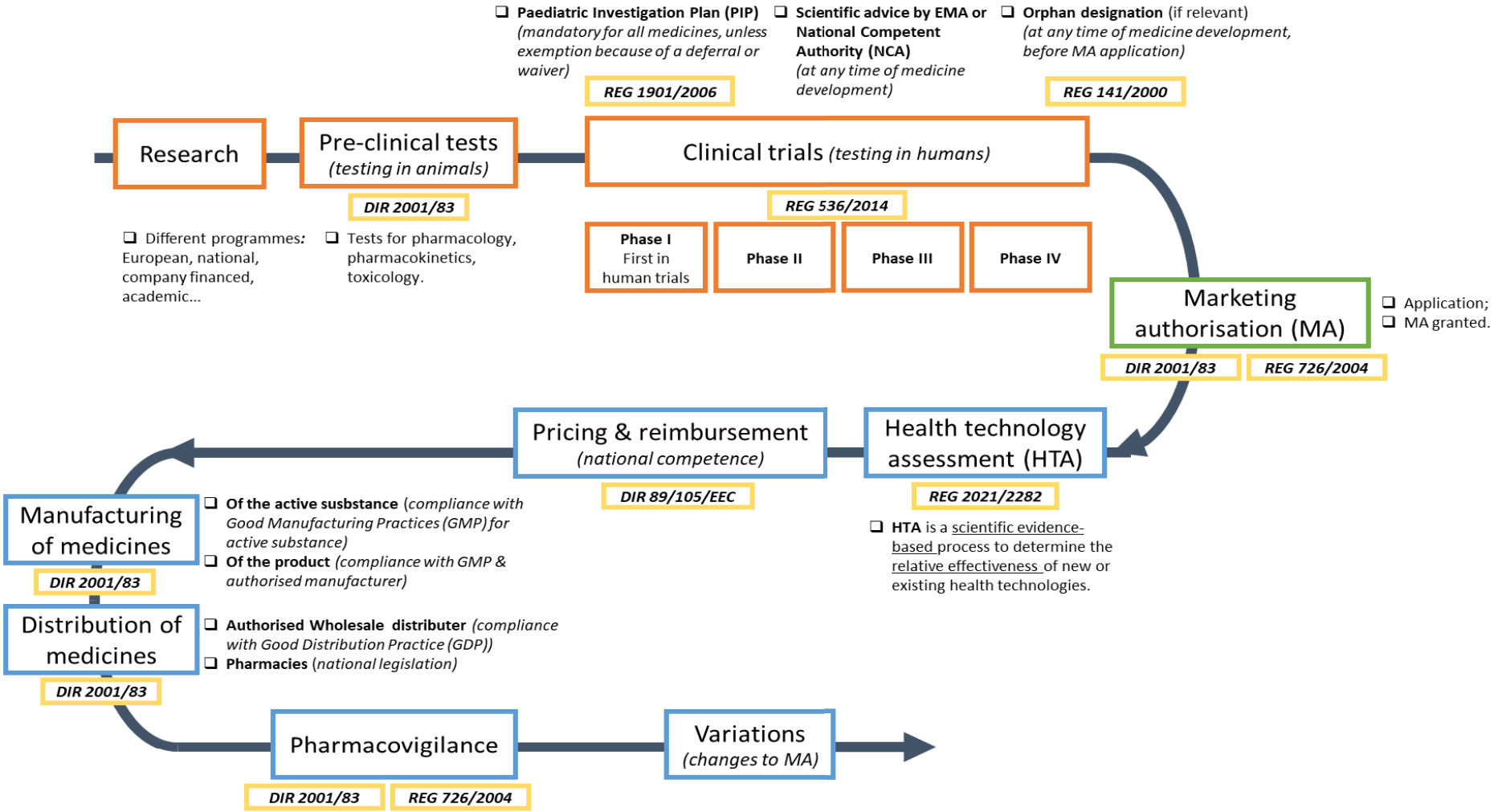
This measure intends to regulate a dysfunctional system. Currently the paediatric regulation offers 6 months SPC extension for completing PIP, and for orphan medicines 2 years of market exclusivity extension. From the entry into force of the Paediatric Regulation up to 2020, only 11 of these market exclusivity extensions were granted. The system has allowed some companies to game the system: there have been cases where companies have abandoned the orphan status of their product at the moment of marketing authorisation in order to benefit from the 6 months SPC extension. This has made difficult for generic products to know exactly when the paediatric protection would expire and consequently to plan accordingly.

- *Facilitations for products addressing UMN*

[240] Download (fda.gov)

Criteria to identify products which have the potential to address unmet medical need of children will be defined in the general pharmaceutical legislation. Products which respond to these criteria will be entitled to increased scientific support by the Agency in the early phases of development and dedicated funding.

ANNEX 6: VISUAL OVERVIEW OF THE LIFE-CYCLE OF A MEDICINAL PRODUCT INCLUDING LINKS TO LEGAL FRAMEWORK



ANNEX 7: OVERVIEW OF ECOSYSTEM AND LEGAL FRAMEWORK

1. The pharmaceutical ecosystem

1.1. General

The Pharmaceutical Strategy for Europe[241] describes the pharmaceutical ecosystem and changes in the landscape that transform industry and medicines development from the old model of chemical blockbuster medicines to biological medicines, advanced therapy medicines, combined medicines with software and personalised medicines. Health data is key to fully exploiting the huge potential of new technologies and digitisation. This vision is echoed in the health ecosystem of the updated European industrial strategy[242].

The EU pharmaceutical ecosystem covers activities from pre-clinical research to manufacturing and includes actors ranging from manufacturers (including medical devices and equipment and personal protective equipment), healthcare services; health tech and related services[243]. Overall, it covers **24.8 million direct jobs**, **493 000 firms** (including 99.7% SMEs) and contributes to **9.5% of EU value added**[244]. The EU provides an attractive market for the pharmaceutical industry, especially with regards to the activities and support provided by the European Medicines Agency and the EU-wide marketing authorisation. These elements are key in attracting R&D to the EU and are regulated by the general pharmaceutical legislation. At global level, the EU health industries are also key players in competition with North America and Asia. As an example, in 2018, North America accounted for 48.9% of global sales of medicines compared to Europe (incl. Switzerland) accounting for 23.2%. The EU also accounts for 24% of the world's API production compared to 65.5% being produced in Asia Pacific. The EU pioneered in sophisticated biologic innovative medicines (and biosimilar medicines), however, Asia and the US are rapidly catching up[245].

In the ecosystem, 'big pharma'[246] are increasingly outsoucing functions, including clinical trials and manufacturing, and are focusing investment on a limited number of therapeutic areas while disinvesting from others[247]. Emerging biopharma companies – often SMEs – are driving a large portion of innovation and development. Emerging biopharma companies were responsible for a record 65% of the molecules in the R&D pipeline in 2021, up from less than 50% in 2016 and 33% in 2001. Top pharmaceutical companies' share of the total R&D pipeline has been shrinking over the last decade (PharmaProjects 2020).

Big pharma is increasingly disinvesting from risker upstream research and instead access products that are already in later clinical trials stages through acquisitions of small biotech

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[241] COM(2020) 761 final.
[242] COM(2021) 350 final European industrial strategy | European Commission (europa.eu).
[243] SWD(2021) 351 final – page 138.
[244] SWD(2021) 351 final – page 137.
[245] SWD(2021)351 final – page 139.
[246] Understood as multinational companies dominating the industry sales and traditionally responsible for all aspects of the medicines discovery pipeline.
[247] European pharmaceutical research and development. STUDY Panel for the Future of Science and Technology. European Parliament Research Service.

companies or start-ups with promising portfolios of patents[248]. Once the molecule reaches a certain maturity (e.g. completing phase II clinical trials) and still looks commercially promising, big pharma companies come in, they partner, buy the molecule or buy the company at the stage of the expensive late-stage clinical trials, marketing authorisation and market launch. Licensing is also used extensively in the pharmaceutical sector, though small firms and start-ups also rely on venture capital to finance their R&D (Kyle 2020).

2. Legal framework

a. Basic legislative acts

The **general EU pharmaceutical legislation** consists of Directive 2001/83/EC and Regulation (EU) No 726/2004 forming one policy intervention. Directive 2001/83/EC provides the framework for authorisation and monitoring of medicines post-authorisation (pharmacovigilance) for nationally authorised medicines, manufacturing and wholesale distribution and authorisation of actors in the supply chain, advertising and falsified medicines. The Regulation establishes the European Medicines Agency and its governance and provides also the framework for authorisation of medicines through a centralised procedure and for pharmacovigilance of these medicines. When it comes to technical requirements for the authorisation application and the lifecycle management of medicines, the Regulation refers regularly to the common requirements in Directive 2001/83/EC.

Medicines may either be authorised centrally by the Commission based on a positive scientific assessment by the European Medicines Agency (EMA), the centralised procedure (CP), or nationally by an individual or a group of Member States. A medicinal product authorised via the CP is not necessarily accessible in all Member States, as its actual placing on the market may depend on the launch strategy of companies and national pricing and reimbursement decisions. Both legal acts are grounded on the fundamental principle that a medicine for human use may only be placed on the market once authorised based on a positive benefit-risk of its quality, safety and efficacy, and that applies regardless of the authorisation procedure.

The specialised legislations for rare diseases and children ("the Orphan and Paediatric Regulations") complement the general EU pharmaceutical legislation (that also apply to medicines for rare diseases and children) to specifically support the development in these previously neglected areas, mainly through specific, additional incentives and obligations. Both the Orphan and Paediatric Regulations are designed to address specific unmet medical

[248] European pharmaceutical research and development. STUDY Panel for the Future of Science and Technology. European Parliament Research Service.

needs of small populations: (i) the Orphan Regulation aims at enabling research, development and authorisation of new medicines for rare diseases through specific incentives and (ii) the Paediatric Regulation works mainly with obligations. It compels companies already developing products for adults to screen them for possible use in children. It provides rewards once this obligation has been fulfilled, to compensate for the additional costs.

The revision of these specialised legislations, also ongoing, follows coherent objectives with the revision of the general pharmaceutical legislation: promoting innovation to better address unmet medical needs, ensuring access of patients to innovative medicines and reducing regulatory burden. Taken together, they aim to ensure the right balance between giving incentives for innovation to strengthen the research base of the EU pharmaceutical industry and the need for patients to have access to affordable medicines.

Advanced therapy medicines[249] are also regulated under specialised legislation. This legislation is also an 'add-on' the general pharmaceutical legislation for this specific product category and concerns in particular technical requirements adapted to the particular characteristics of these products, special incentives for SMEs and their assessment. The legislation on advanced therapy medicines is not subject to revision and as such not in the scope of this impact assessment.

These legislations are complemented by more specific ones, applicable at different stages of the lifecycle of medicines.

b. Other legislative acts and policies applicable to medicinal products

i. At the research and development stage

The Regulation on clinical trials[28] harmonises the processes for the assessment and supervision of clinical trials throughout the EU. The evaluation, authorisation and supervision of clinical trials are the responsibilities of Member States and the Regulation ensures harmonisation. The regulation also allows as of 2022 a more efficient process for the approval of multinational trials. Having a single application and a single package will streamline the registration, assessment and supervision processes for EU clinical trials. This will also facilitate the conduct of trials in small populations scattered in several countries.

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[249] Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004, OJ L 321, 10.12.2007, p. 121, LexUriServ.do (europa.eu).

The **proposed Regulation on the European Health Data Space** (EHDS)[250] will provide a common framework across EU Member States for access to quality health data for use in research and development of new treatments.

The **European innovation Council** (EIC)[251] established under the Horizon 2020 programme aims at identifying and supporting breakthrough technologies and game changing innovations with the potential to scale up internationally and become market leaders. It supports all stages of innovation from R&D on the scientific underpinnings of breakthrough technologies, to validation and demonstration of breakthrough technologies and innovations to meet real world needs, to the development and scaling up of start-ups and small and medium-sized enterprises (SMEs).

The **Innovative Health Initiative Joint Undertaking**[252] (IHI JU) is a public-private partnership between the European Union, represented by the European Commission, and several health industries from the biopharmaceutical, biotechnology and medical technology sectors. IHI brings together diverse stakeholders (universities, companies large and small, and other health stakeholders) in collaborative projects that address disease areas where there is a high burden on patients and/or society. The initiative focuses on cross-sectoral projects supporting the development of safe, effective, people-centred and cost-effective products and services that target key unmet public health needs.

ii. At the authorisation stage

The authorisation procedures are laid down in the general pharmaceutical legislation but aspects linked to authorisation are completed by other regulations.

Beyond the **general patent rules** applicable to medicines, the **Regulations on supplementary protection certificates (SPCs)**[253] provide for supplementary intellectual property rights extending patent protection for specific medicines. SPCs aim to offset the loss of patent protection for medicines that occurs due to the compulsory lengthy testing and clinical trials these products require prior to obtaining marketing authorisation.

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[250] Proposal for a Regulation of the European Parliament and of the Council on the European Health Data Space, COM(2022) 197 final, Proposal for a regulation - The European Health Data Space (europa.eu).

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

[252] Council Regulation (EU) 2021/2085 of 19 November 2021 establishing the Joint Undertakings under Horizon Europe and repealing Regulations (EC) No 219/2007, (EU) No 557/2014, (EU) No 558/2014, (EU) No 559/2014, (EU) No 560/2014, (EU) No 561/2014 and (EU) No 642/2014, OJ L 427, 30.11.2021, p. 17, EUR-Lex - 32021R2085 - EN - EUR-Lex (europa.eu)

[253] Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the supplementary protection certificate for medicinal products, OJ L 152, 16.6.2009, p. 1, EUR-Lex - 32009R0469 - EN - EUR-Lex (europa.eu) and Regulation (EU) 2019/933 of the European Parliament and of the Council of 20 May 2019 amending Regulation (EC) No 469/2009 concerning the supplementary protection certificate for medicinal products, OJ L 153, 11.6.2019, p. 1, EUR-Lex - 32019R0933 - EN - EUR-Lex (europa.eu).

Table 41 - Overview of the current IP and regulatory protection incentives for medicines

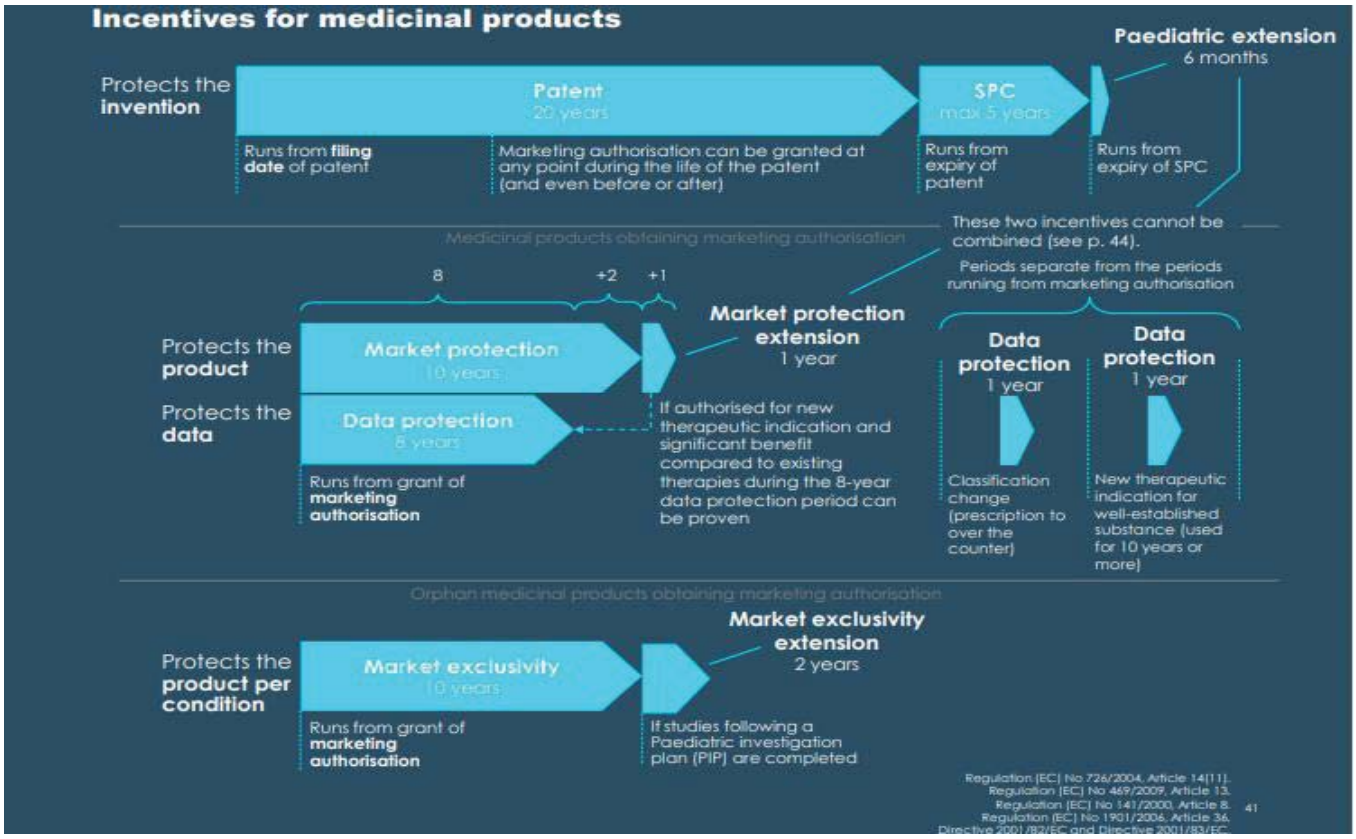

Table 41 above provides an overview[254] of the current IP and regulatory protection rules for medicines in the EU.

The ongoing review of the SPC regulation[255] will put in place a unitary SPC and/or a single ('unified') procedure for granting national SPCs. This will make SPCs more accessible and efficient, and will impact the health sector.

iii. At the market launch stage

Following marketing authorisation companies take decisions on the market launch in Member States based on commercial considerations[256]. These decisions are influenced by the

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[254] Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe - Copenhagen Economics (2018)

[255] Medicinal & plant protection products – single procedure for the granting of SPCs (europa.eu).

[256] The authorisation of a medicinal product does not mean that it will be immediately accessible to all European patients. Factors such as the size of the population or the organisation of health systems and national procedures influence these decisions. Companies tend to begin negotiations with the Member States that may grant a higher

national decisions on pricing and reimbursement of the medicines concerned, since pricing and reimbursement is the competence of Members States[257].

The **Directive on transparency of measures regulating the prices of medicines** and their inclusion in the scope of national health insurance systems[258] aims at obtaining an overall view of national pricing arrangements, and providing public access to them for all those involved. This Directive regulates the procedural aspects of the Member States' decisions on pricing and reimbursement, e.g. timelines for decisions on pricing and reimbursement, publication of criteria for reimbursement and negative reimbursement decisions have to be justified. It does not impact on the level of price.

To help national authorities in their reimbursement decisions national Health Technology Assessment (HTA) bodies may assess the medicines. The HTA is a scientific evidence-based process to determine the relative effectiveness of new or existing health technologies.

The **Regulation on HTA**[259] establishes a Coordination Group of HTA national or regional authorities, a stakeholder network and lays down rules on the involvement in joint clinical assessments and joint scientific consultations of patients, clinical experts and other relevant experts. The regulation also reduces duplication of efforts for national HTA bodies and industry, facilitates business predictability and ensures the long-term sustainability of EU HTA cooperation. The new rules will come in to force in 2025 and should complement the efforts of the EU general pharmaceutical legislation to incentivise innovation with a strengthened and expanded HTA capacity.

iv. After the market launch stage

Once a medicine is authorised and placed on the market, it is subject to pharmacovigilance. Pharmacovigilance relates to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem. The general EU pharmaceutical legislation details the pharmacovigilance obligations.

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price, often the countries with the highest GDP per capita. The willingness to pay a high(er) price in a Member State with a high GDP may limit the ability of a smaller Member State to negotiate a price in line with its GDP; hence, differences in the accessibility and affordability across the EU.

[257] The decision for pricing and reimbursement is based on national policies, which pertain to Member States and thus are outside the remit of the EU legislation and of this revision.

[258] Council Directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of national health insurance systems, OJ L 40, 11.2.1989, p. 8, EUR-Lex - 31989L0105 - EN - EUR-Lex (europa.eu).

[259] Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU, OJ L 458, 22.12.2021, p. 1, EUR-Lex - 32021R2282 - EN - EUR-Lex (europa.eu).

In addition, the **Regulation on the performance of pharmacovigilance activities**[260] outlines the practical details to be respected by marketing authorisation holders, national competent authorities and the EMA and the **Regulation on post-authorisation efficacy studies**[261] specifies the situations in which such studies may be required.

After an initial authorisation has been granted, market authorisation holders can also develop changes to the medicines. The **Regulation on variations**[262] sets the procedures for post-authorisation changes to a marketing authorisation for medicines. These changes can e.g. be changes in address of the company, active substance, strength, pharmaceutical form or route of administration. The Commission also intends to review this regulation so as simplify the system and reduce administrative burden for medicine authorities and companies.

c. Legislation in adjacent areas

The **legal framework for blood, tissues and cells**[263] (BTC) is used for medical treatments and therapies, including innovative therapies. The ongoing review will promote the safety of patients and donors, facilitate innovation and contribute to adequate supply of the relevant therapies. Blood, tissues and cells may be starting materials for medicines. Particularly important for the pharmaceutical sector is the strengthening the safety and quality requirements of BTC to align with the standards of the pharmaceutical framework for the highest risk preparations. It will also address the (re)emergence of communicable diseases, including lessons learnt from the COVID-19 pandemic, and is thus contributing to the European Health Union.

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[260] Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council, OJ L 159, 20.6.2012, p. 5, EUR-Lex - 32012R0520 - EN - EUR-Lex (europa.eu).

[261] Commission Delegated Regulation (EU) No 357/2014 of 3 February 2014 supplementing Directive 2001/83/EC of the European Parliament and of the Council and Regulation (EC) No 726/2004 of the European Parliament and of the Council as regards situations in which post-authorisation efficacy studies may be required, OJ L 107, 10.4.2014, p. 1–4, EUR-Lex - 32012R0520 - EN - EUR-Lex (europa.eu).

[262] Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products, OJ L 334, 12.12.2008, p. 7, EUR-Lex - 32008R1234 - EN - EUR-Lex (europa.eu).

[263] Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC, OJ L 33, 8.2.2003, p. 30, EUR-Lex - 32002L0098 - EN - EUR-Lex (europa.eu) and Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, OJ L 102, 7.4.2004, p. 48, EUR-Lex - 32004L0023 - EN - EUR-Lex (europa.eu).

The **regulation on medical devices**[264] and **the regulation on in vitro diagnostic medical devices**[265] deal with medical devices, which are products or equipment intended for a medical purpose. In the EU, they must undergo a conformity assessment to demonstrate they meet legal requirements to ensure they are safe and perform as intended. They are assessed at Member State level, but EMA is involved in the assessment sometimes. In some cases, the bodies responsible for the conformity assessment must seek a scientific opinion from EMA before issuing a CE certificate. This is the case essentially when medicines are concerned (e.g. medical devices with an ancillary medicinal substance, companion diagnostics). In some other cases (when the device in ancillary to the medicines), the combined product requires a marketing authorisation.

[264] Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC, OJ L 117, 5.5.2017, p. 1, EUR-Lex - 02017R0745-20200424 - EN - EUR-Lex (europa.eu).

[265] Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU, OJ L 117, 5.5.2017, p. 176, EUR-Lex - 02017R0746-20170505 - EN - EUR-Lex (europa.eu).

ANNEX 8: INTERNATIONAL CONTEXT

Table 42 **- Comparison of criteria for orphan designation in the EU, US and Japan**

	EU	US	Japan
Orphan condition	< 5 in 10,000 in EEA; OR without incentives it is unlikely that the marketing would generate sufficient return to justify the investment.	≤ 6 in 10,000 in US; OR an orphan subset of a non-rare disease; condition where the characteristics of the medicinal product limit its use in a particular subgroup; OR	< 4 in 10,000 in Japan;
Medical need	No satisfactory methods of treatment (or prevention or diagnosis) for life-threatening or chronically debilitating condition exist; OR if any such methods exist the medicinal product must be of significant benefit to those affected by the condition, i.e.: o conferring a clinically relevant advantage; OR o a major contribution to patient care.	Not a criterion unless the same drug has previously been approved for the same use or indication, clinical superiority needs to be proven as follows: Shown to provide a significant therapeutic advantage over an approved drug in one or more of the following ways: (i) Greater effectiveness; (ii) Greater safety in a substantial portion of the target populations; (iii) In unusual cases, where neither greater safety nor greater effectiveness has been shown, a demonstration that the drug otherwise makes a major contribution to patient care.	No appropriate alternative drug/medical device treatment for serious disease including difficult to treat the disease; OR higher efficacy or safety is expected compared with existing products.
Medical plausibility/ scientific rationale	Usually *in vivo* data.	Clinical study data or case reports if available; *in vivo* animal data; *in vitro* data if no clinical or *in vivo* data available	Non-clinical and clinical data in the latter half of the phase I study or in the first half of the phase II study.

TABLE 43 - KEY DIFFERENCES IN THE PROCEDURES FOR ORPHAN DESIGNATION IN THE EU, US AND JAPAN[266]

Items	EU	US	Japan
Application to	Committee for Orphan Medicinal Products (COMP).	Office of Orphan Products Development (OOPD).	Ministry of Health, Labour and Welfare (MHLW)
Timetable	Timetable for submission and assessment published by the Agency.	Any time; no defined timetable;	Any time; no defined timetable;
Key aspects of the application	Prevalence; Medical need; Medical plausibility.	Prevalence. Scientific rationale.	Prevalence; Medical need; Possibility of development.
Sponsor established in territory	Proof of establishment in EU.	Not required.	Not required.
Translations	Translations of product name and proposed orphan indication into all official languages of the EU plus Icelandic and Norwegian.	Not required.	Application in Japanese.

[266] In the US, a medicinal product is eligible for orphan designation when it is intended to treat a disease that affects less than 200 000 persons (which is equivalent to 6 in 10,000) in the US or affects more than 200 000 persons and for which there is no reasonable expectation that the cost of developing and making a medicinal product for such disease or condition will be recovered from sales. In addition, in the US an orphan designation may be given to an orphan subset of a non-rare disease condition where the characteristics of the medicinal product limit its use in a particular subgroup. O'Connor DJ; Expert Opinion on Orphan Drugs (2013), 1(4):255-259.

ANNEX 9: CRITERIA TO IDENTIFY PRODUCTS ADDRESSING UMN AND HUMN

	High UMN **Orphan** medicinal products	UMN **general** pharmaceutical legislation[267]
CRITERIA		
Disease level	Life-threatening or seriously debilitating	Life threatening or seriously debilitating
Product level	[Criteria for designation continue to apply - Article 3 of the Orphan Regulation: <5 in 10 thousand persons in the Community] <u>Case 1</u> • **No medicine is authorised** for the treatment of the disease/condition; **And** • There is **no commonly used (non-pharmacological) method** of treatment whether subject to marketing authorisation or not (e.g. surgery). **And** • The treatment concerns the substantial part of population affected by the orphan disease; **And** • The product does not concern a well-established use product. **[OR]** <u>Case 2</u> • **Treatments exist** but they: - Are symptomatic, not curative; **And** • The treatment under development is a **curative** treatment for the majority of patients affected by the orphan disease.	<u>Case 1</u> • **No medicine is authorised** for the treatment of the disease/condition; **<u>[OR]</u>** <u>Case 2</u> • Medicines are authorised but are not **satisfactory** o Remaining high morbidity or mortality, [or] o Serve less than a certain % of the population affected by the disease, [or] o There is no paediatric indication. **And** <u>In both cases (1 and 2), the new product must:</u> - Have a large treatment effect (reducing morbidity or mortality); [**and**] - Serve a substantial part of population; **[OR]** <u>Case 3</u> - It concerns an **orphan designated medicinal product** that automatically fulfils UMN for general pharma (meaning there is no additional requirement(s))

[267] Criteria applicable also for medicines for children

ANNEX 10: FACTORS INFLUENCING ACCESS TO AFFORDABLE MEDICINES

This annex sets out the different regulatory steps and related decision making processes that have an impact on access and affordability of medicines ("access chain"). Section 1 describes the different steps in the "access chain" from authorisation of medicines to patient access. Section 2 provides further details on pricing and reimbursement policies across the EU and how they can influence access to affordable medicines.

1. **The access chain: from market authorisation of medicines to patient access**

Marketing authorisation is but the first of a number of steps for patients to have access to a medicine. Patient access also requires, following relevant applications by companies, positive HTA assessments and positive pricing and reimbursement decisions by Member States. In addition to those steps, for patients to have access *across the entire EU*, companies have to launch the respective medicine in each Member State. Finally, for a patient to have actual access to a medicinal product, a prescriber has to decide that a medicine is the right treatment choice and prescribe it. The steps from marketing authorisation to patient access can be described along an access chain, which is summarised in the table below. Further details on each step are provided in the following subsections of this section.

Table 44 - Overview *of the access chain: marketing authorisation to patient access*

STEPS	Scope	Legal framework
1. Marketing authorisation	Quality, safety, efficacy; Positive benefit-risk balance	General pharma framework
2. EU-level Health Technology Assessment (clinical HTA aspects)	Relative clinical effectiveness and relative safety, in comparison to comparator treatment(s) reflecting the standard of care; Supports conclusions on added therapeutic (clinical) value	Regulation (EU) 2021/2282
3. Company decision to launch the medicine in a Member State	Submission of application by the company to national HTA, pricing and reimbursement bodies	

4. National Health Technology Assessment	Takes into account the EU-level assessment of clinical HTA aspects; Focuses on context-specific, non-clinical HTA aspects (e.g. economic, organisational); Supports conclusions on cost-effectiveness, budget impact, value for money	National/regional legislation
5. National pricing and reimbursement	Decisions on reimbursement and pricing; Takes into account added therapeutic (clinical) value, economic considerations (cost-effectiveness, budget impact, affordability), healthcare system and societal context	National/regional legislation Directive 89/105/EEC (covering only timeline, process)
6. Prescription	Evidence-based medicine, taking into account clinical guidelines and medical protocols and the individual patient situation	

1.1 Marketing authorisation

For the marketing authorisation of a medicine, the regulator will consider the quality, safety and efficacy of the medicine and authorise it if the medicine has a positive benefit-risk balance for the patient. Accordingly, data requirements for marketing authorisation reflect the need to show quality, safety and efficacy of a particular medicine. "Downstream" steps in the access chain (health technology assessment, pricing and reimbursement) often require additional data to show an added value of a newly authorised medicine compared to already existing medicines/treatments (see sections 1.2, 1.4 and 1.5).

It should however be noted though that even medicines which appear similar at the time of launch may over time prove to have different efficacy or safety profiles in particular subgroups of patients. Furthermore, the effect of treatment in individual patients may differ from the population-level effects seen in clinical trials. With greater choice, patients will have a better chance of finding a treatment most appropriate to their needs. For these reasons, EU regulations on marketing authorisation do not require that new medicines be superior to medicines already on the market.

1.2 EU-level Health Technology Assessment (clinical HTA aspects)

Health technology assessment (HTA) evaluates the added value of a new medicine in comparison to existing medicines (or other treatments) that reflect the current standard of care. HTA is an evidence-based approach that helps Member States to provide the optimal health care outcome for patients with limited budgets. Accordingly, HTA is used by Member States across the EU in particular for innovative and costly medicines, as a tool to support pricing and reimbursement decisions. However, there is considerable diversity across Member State HTA systems in terms of procedural frameworks, methodological approaches, and available resources and expertise.

In 2022, Regulation (EU) 2021/2282 on health technology assessment entered into force. It provides a legal framework for strengthened EU cooperation on HTA, focusing on clinical aspects of HTA (including the development of common methodologies). From 2025 onwards, Member State HTA bodies will jointly assess *clinical* HTA aspects (comparative clinical effectiveness and safety) of centrally authorised innovative medicines (Joint Clinical Assessment).[268] Such Joint Clinical Assessments will have to be taken into account by Member States in their national HTA processes. Joint Clinical Assessments will be high quality, timely scientific reports (available within 30 days from marketing authorisation). They will enable Member States to focus their limited national HTA resources on assessing more context-specific, non-clinical aspects of HTA (see section 1.4).

Clinical data generated for marketing authorisation purposes (to demonstrate safety and efficacy of the individual product) are not always considered sufficient for HTA and down-stream pricing and reimbursement purposes, which rely on demonstration of comparative effectiveness and safety (i.e. added therapeutic value over existing medicines/treatments).[269,270,271] HTA bodies generally require clinical trials that include an active comparator arm (rather than a placebo-controlled trial or a single-arm trial). HTA bodies also often see challenges with clinical trial data that are less mature and come with higher uncertainties, e.g. in the context of conditional marketing authorisations.[272] When HTA bodies consider the available clinical data inappropriate or insufficient for demonstrating an added therapeutic value, this can lead to delays and

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[268] Step-wise implementation of the product scope: oncology and advanced therapy medicines from 2025, orphan medicines from 2028, all centrally authorised innovative medicines (new active substances) from 2030.

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

[270] Bloem LT, Mantel-Teeuwisse AK, Leufkens HGM, De Bruin ML, Klungel OH, Hoekman J. Postauthorization Changes to Specific Obligations of Conditionally Authorized Medicines in the European Union: A Retrospective Cohort Study. Clin Pharmacol Ther. 2019;105(2):426-35.

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

[272] In the interest of public health, a conditional marketing authorisation may be granted for such medicines on less comprehensive clinical data than normally required subject to legally binding obligations for the marketing authorisation holder to generate the comprehensive data after the authorisation.

negative results in the downstream decision-making process on pricing and reimbursement.[273, 270, 271]

From a company perspective, the conduct of clinical trials that generate the comparative evidence required for HTA purposes can be more risky, more costly or take longer. Companies have also faced challenges related to lack of clarity on data needs for HTA, given the diversity of HTA systems and methodological frameworks across Member States. Companies have therefore traditionally (first) focused on the data needs for marketing authorisation when designing their clinical trials. This is however changing and there have been increasing calls by pharmaceutical companies and other stakeholders for more early dialogues on evidence needs along the lifecycle of products and for scientific advice on evidence generation.[270, 271]

For this reason, the new HTA Regulation (Regulation (EU) 2021/2282) provides also a legal framework for scientific advice by HTA bodies to companies on clinical trial design (common HTA advice, agreed at the level of the Member State Coordination Group on HTA), in parallel with scientific advice by the European Medicines Agency provided for marketing authorisation purposes. While respecting the different remits of marketing authorisation and HTA, this parallel scientific advice aims to ensure the generation of evidence that meets the requirements of both frameworks. Parallel scientific advice has already been successfully piloted in the context of EU-funded projects (in particular the Joint Actions EUnetHTA in cooperation with EMA).[274]

1.3 Company decision to launch the medicine in a Member State

It should be noted that while a marketing authorisation at EU level allows for a medicine to be placed on the market in all Member States, the actual market launch in a given Member State is exclusively the decision of the marketing authorisation holder. Company decisions are commercial decisions that take into account whether there is a 'market' for the medicine in a given Member State from a business point of view, considering factors such as market size, price levels, promotion and distribution networks, regulatory requirements, current or future patient population, medical protocols and national pricing and reimbursement policies such as external reference pricing (see Section 2 on pricing and reimbursement policies for further details). Factors related to the healthcare system can also influence the decision, e.g. the availability of specialised equipment or infrastructure to deliver the medicine (in particular in the case of advanced therapy medicines), or national treatment preferences. If the conditions for a positive business case are met, the company will initiate the procedures required for

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[273] Vreman RA, Bouvy JC, Bloem LT, Hövels AM, Mantel-Teeuwisse AK, Leufkens HGM, Goettsch WG. Weighing of Evidence by Health Technology Assessment Bodies: Retrospective Study of Reimbursement Recommendations for Conditionally Approved Drugs. Clin Pharmacol Ther. 2019 Mar;105(3):684-691. doi: 10.1002/cpt.1251. Epub 2018 Nov 8. PMID: 30300938; PMCID: PMC6587700.

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

market launch in that Member State (by submitting applications for HTA, pricing and reimbursement, in accordance with national legal/procedural frameworks).

Smaller and less wealthy countries will often see fewer product entries (due to smaller market potentials). For these countries, the time to availability is also significantly longer. The average time to market from marketing authorisation in Europe differs greatly: for example, for cancer drugs, in the period 2011-2018, it ranged from 17 to 1.187 days, with the shortest delays in Germany, the UK and Austria (less than 31 days) and the longest delays in Greece and Estonia (more than 950 days).[275] In other cases, medicines became available in Central and Eastern Europe only several years after marketing authorisation[276], with market launch delayed up to three years on average in Central-Eastern Europe.[277] It should however be noted that a lack of access to a specific medicine does not necessarily imply lack of access to effective treatment, if appropriate therapeutic alternatives are accessible.[278]

1.4 National Health Technology Assessment

For medicines for which HTA is conducted to support pricing and reimbursement decisions (usually for innovative, costly medicines), the national HTA procedure is usually triggered by marketing authorisation holders launching a pricing and reimbursement application in the Member State concerned.

Currently, HTA bodies assess both clinical aspects (comparative effectiveness and safety) and non-clinical aspects (e.g. economic, organisational, social, ethical) at national level. From 2025 onwards, assessments of clinical HTA aspects will be conducted jointly at EU level (Regulation (EU) 2021/2282), and HTA work at national level is expected to focus on non-clinical HTA aspects (see section 1.2). Clinical HTA analyses support pricing and reimbursement authorities in drawing conclusions on added therapeutic value, while economic HTA analyses support them in concluding on cost-effectiveness, value for money and budget impact.

1.5 National pricing and reimbursement decision

Pricing and reimbursement rules and policies are an exclusive competence of Member States (Article 168 TFEU). Due to historical, political, legal and economic developments, a large variety in pricing and reimbursement regulations have developed across Member States. Moreover, the overall organisation and funding of national healthcare systems differ significantly.279

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[275] Uyl-de Groot, C., Heine, R., Krol, M., and Verweij, J. 'Unequal Access to Newly Registered Cancer Drugs Leads to Potential Loss of Life-Years in Europe, Cancers, 2020.
[276] Vogler, S., Schneider, P., and Zimmermann, N., 'Evolution of Average European Medicine Prices: Implications for the Methodology of External Price Referencing', PharmacoEconomics, 303-309, 2019.
[277] Maini, L., & Pammolli, F., Reference Pricing as a Deterrent to Entry: Evidence from the European Pharmaceutical Market, 2017.
[278] OECD (2018), Pharmaceutical Innovation and Access to Medicines, OECD Health Policy Studies, OECD Publishing, Paris, https://doi.org/10.1787/9789264307391-en.
[279] Health System in Transition Reviews (HiT) (who.int)

National and/or regional pricing and reimbursement policies assess the size of the patient population and budget impacts, and negotiate the price. Often, late market entries in some Member States are driven by a combination of business decisions and national pricing/reimbursement policies, such as external reference pricing, leading marketing authorisation holders to market their medicines first in Member States where a high price can be obtained (see section 2 on pricing and reimbursement policies across the EU for further details). Some Member States, e.g. Greece, require proof of a positive reimbursement decision in comparable countries before an HTA assessment can be initiated.280

Pharmaceutical expenditure is largely subsidised by national health systems in order to ensure the adequate provision of medicines to all citizens. In this context, Member States adopt measures to regulate the prices of medicines and the conditions of their public funding. Such measures influence the prescription and utilisation of medicines in each Member State and also affect the decisions of and possibilities for pharmaceutical companies to sell their products in national markets. Industry stakeholders claim delays in national pricing and reimbursement decisions that would contribute to postponing the market entry of medicines after the granting of a (central) marketing authorisation. However, a factor that can contribute to delays in national pricing and reimbursement decisions is a lack of appropriate evidence on the added therapeutic value of the product, or evidence that suggests only a minor added therapeutic value (see sections 1.2, 1.4 and 2.2).

Directive 89/105/EEC ('Transparency Directive') is the only EU legal instrument in relation to the applicable national rules on pricing and reimbursement of medicines. The Directive is built on the principle of minimum interference in the organisation of national social security systems. It lays down a series of procedural requirements to ensure the transparency of national decisions on pricing and reimbursement, such as a timeline of 180 days (with the possibility of extension or suspension of the timelines), and procedures such as requirements for publishing the outcomes of national decisions. In light of the Treaty rules on free movement of goods (Article 34 TFEU), the Directive has the objective to avoid barriers to trade created by national measures.[281]

It should be noted that the Transparency Directive refers to the transparency of the pricing and reimbursement process, but not the transparency of prices. In general, prices are publicly available only in form of 'list prices'. These list prices are increasingly disconnected from the actual prices paid. Typically and in particular for products with high price and high uncertainty, confidential price discounts[282] or managed entry

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[280] Kourlaba, Georgia & Beletsi, Alexandra. (2021). Time to Patients' Access to New Medicines in Greece: Evaluation of Health Technology Assessment (HTA) Process from July 2018 until January 2021.

[281] An update of the Directive had been proposed by the European Commission in 2012, however it was officially withdrawn in 2015. A dedicated study will be launched in 2023 to take stock of the implementation challenges and to explore how Directive 89/105/EEC could further contribute to the affordability objectives of the Pharmaceutical Strategy.

[282] There is little public data on confidential prices; however there are indications that it may be broadly on average around 20% of the pharmaceutical budget, with high variation across products and countries. Steven G. Morgan, Sabine Vogler, Anita K. Wagner, Payers' experiences with confidential pharmaceutical

agreements are in place (see section 2 on pricing and reimbursement policies). In a 2022 working paper, the OECD summarised the complex impacts of the **lack of price transparency**: "*It can be argued that confidentiality assists payers in achieving more favourable net prices, and companies in price discriminating between countries, which promotes equitable access [...]. At the same time, however, confidentiality is undermining the confidence of both payers and patients about the industry, and further challenging policy makers in attempting to find a balance between rewarding innovation, delivering affordable access, and maintaining the sustainability of health systems.*"[283]

1.6 Prescription and use

For a patient to have access to prescription medicines, a prescriber will first have to consider whether this medicine is the appropriate choice for the patient. Then, the patient will need to accept and adhere to the proposed treatment. Prescribers make an informed choice based on clinical guidelines or treatment protocols that provide information on the added clinical benefit of the available treatment options and support the identification of a first line choice. Clinical guidelines sometimes take into consideration the affordability to health systems and patients. Inclusion of a medicine in clinical guidelines and treatment protocols is an important factor influencing a company's decision to launch a medicine in a given market. The prescription of medicines can also be influenced by industry promotion and detailing. A company will seek to gain prescriptions by actively differentiating its product from alternative treatments, through promotion activities vis-à-vis doctors, training of nurses, patient support programmes, etc.

1.7 *Alternative access chains*

The health impact of late market entries is mitigated by the fact that innovative therapies are often accessible for patients through exceptions, such as compassionate use/named patient use schemes. Some countries have established "(innovation) funds" for defined medicines which are expensive but still considered important for patients, so they are financed out of funds that bypass the "standard" reimbursement processes. Furthermore, a medicine may be brought to a national market outside the national reimbursement scheme and will need to be paid for by private insurance or out-of-pocket payments. Depending on the national health systems, medicines may enter the market without national pricing or reimbursement decisions. This would be the case for many non-prescription medicines. However, in the absence of a reimbursement decision, the patient has to pay to out-of-pocket.

2. Pricing and reimbursement policies across the EU

Member States have developed a large variety of pricing and reimbursement institutional frameworks and policies, some of which are explained in further detail below.[284] While there are overviews and comparisons of the different systems, the impact of the different organisational systems on access and affordability is complex and has not yet been modelled in a comprehensive way.

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price discounts: A survey of public and statutory health systems in North America, Europe, and Australasia, Health Policy, Volume 121, Issue 4, 2017, Pages 354-362, ISSN 0168-8510.

[283] OECD Health Working paper 146. Exploring the consequences of greater price transparency on the dynamics of pharmaceutical markets. 2022. c9250e17-en.pdf (oecd-ilibrary.org)

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

Regarding the institutional framework, a wide variety of different organisations and structures have been set up in the various EU Member States. The organisations responsible for marketing authorisation, health technology assessment and pricing and reimbursement may be part of the same organisation (e.g. Portugal, Cyprus, Czechia), organised decentrally (e.g. Denmark, Spain, Italy), combining regulatory and HTA functions (Finland, Hungary) or combining pricing and/or reimbursement and HTA functions (Latvia, Luxembourg, Malta, Netherlands).[285]

2.1 External reference pricing

The large majority of Member States apply, amongst others, external reference pricing (ERP), which considers a basket of prices of the same medicine in other countries (e.g., the average, or the average of a certain number of the lowest prices, or the lowest price) as a basis for pricing – and sometimes also reimbursement – decisions[286]. Considering that ERP strongly influences national prices, it has a direct impact on any companies' business case for launching medicines in different national markets. Accordingly, ERP influences also the path of launch of medicines across Europe.

Sequencing of market entry in the EU – typical patterns of pharmaceutical companies

Marketing authorisation holders choose the sequence of market entry to maximise their gains and limit the spill-over of lower prices in a given Member State on another Member State. There are fixed costs associated with entering a national market (e.g., procedural, or related to the packaging). Pharmaceutical companies primarily focus on Member States with significant market potential, taking into account the population size and the public pharmaceutical budget per capita. Companies set their prices based on the market conditions in Member States with greater market potential and purchasing power, not necessarily considering the affordability for lower income countries.[287] Overall, pharmaceutical companies tend to launch their medicines (first) in northern and western Member States with high purchasing power. The sequence of launch typically starts in Germany, where there is free pricing in the first year[288], followed by other large markets with high purchasing power, such as Italy, France, Spain, or smaller markets with high price levels, such as Denmark, Sweden or Luxemburg. To limit the spill-over effects resulting from the ERP system, the marketing authorisation holders

[285] Mapping of HTA national organisations, programmes and processes in EU and Norway (Study by European Commission)
[286] Euripid Guidance Document on External Reference Pricing (ERP)
[287] Access to high-priced medicines in lower-income countries in the WHO European Region
[288] Once a medicine receives marketing authorisation, it can be launched on the German market at a price determined by the pharmaceutical company. An HTA is conducted during the first year as a basis for negotiations on the price that will be reimbursed from the thirteenth month. If the negotiated reimbursement price is below the price charged during the first year, no payback is required from the company. Payer Policies To Support Innovation and Access To Medicines in the Who European Region – WHO OMI technical report - https://www.who.int/europe/publications/i/item/9789289058247

and public authorities have to agree on confidential prices, while maintaining higher list prices. ERP applies to list prices, and is detrimental to transparency of prices. While ERP may improve affordability, it can have an impact on accessibility. For instance, the Slovak Ministry of Health allowed for a 10% higher launch price than reference pricing countries so that pharmaceutical companies would not delay launching. Evidence shows that manufacturers often delay market access to Belgium to avoid creating a Belgian reference price – as it is typically not among the highest in the EU.[289]

2.2 Value based pricing

Another common method is the **value based pricing**, which implies that prices are formed by reference to a medicine's value (value for money). Value is most often measured by cost per QALY (quality adjusted life years). Some medicines may have a low cost per QALY and would be considered good value for money. Medicines with a high cost per QALY would not be considered good value for money. To give an idea of the range of values, prevention and vaccination have typically a low cost per QALY (from 500-5000 EUR e.g. HPV vaccination, maternal vaccination for pertussis), whereas certain interventions have systematically higher QALYs (e.g. end-of life oncology treatments, rare diseases can be over 100 000 EUR/QALY).[290, 291] In these cases, there is a political and ethical choice to be made (whether a QALY is a QALY, no matter to whom it accrues). However, QALYs are easier to interpret when comparing interventions to the same person – to prioritise treatments that bring more benefits (at a lower cost/QALY) to the same patient. Explicit thresholds are in place in e.g. Poland, Hungary, Slovakia and Ireland[292] – around the range of 30 000 - 50 000 EUR/QALY. A debate about pros and cons is recurrent[293] – a major downside is that regardless of the R&D and production costs, the value-based price would tend to be set at the relevant threshold.[294]

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[289] Fontrier, AM., Gill, J. & Kanavos, P. International impact of external reference pricing: should national policy-makers care?. Eur J Health Econ 20, 1147–1164 (2019).

[290] Kocot, E., Kotarba, P. & Dubas-Jakóbczyk, K. The application of the QALY measure in the assessment of the effects of health interventions on an older population: a systematic scoping review. *Arch Public Health* 79, 201 (2021). https://doi.org/10.1186/s13690-021-00729-7

[291] Postma, M.J., Noone, D., Rozenbaum, M.H. *et al.* Assessing the value of orphan drugs using conventional cost-effectiveness analysis: Is it fit for purpose?. *Orphanet J Rare Dis* 17, 157 (2022). https://doi.org/10.1186/s13023-022-02283-z

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

[293] Bertram, M. Y., Lauer, J. A., De Joncheere, K., Edejer, T., Hutubessy, R., Kieny, M. P., & Hill, S. R. (2016). Cost-effectiveness thresholds: pros and cons. *Bulletin of the World Health Organization*, *94*(12), 925–930. https://doi.org/10.2471/BLT.15.164418

[294] Such process can be observed in oncology medicines, Howard et al. (2015) document price increases in the anticancer medicines market of about 10% a year in the past 20 years, after controlling for increased benefits (survival). Cost changes are deemed unlikely to be behind the price increases. David H. Howard & Peter B. Bach & Ernst R. Berndt & Rena M. Conti, 2015. "Pricing in the Market for Anticancer Drugs," Journal of Economic Perspectives, vol 29(1), pages 139-162.

While innovative medicines receive marketing authorisation on the basis of an evaluation of their quality, efficacy and safety and a positive benefit-risk balance, as explained, downstream actors (HTA bodies and pricing and reimbursement authorities) require evidence on therapeutic added value (see section 1 on the access chain). Several studies across multiple indications and countries (e.g. Germany[295], France, or Italy[296]) suggest that a significant percentage of innovative medicines come to the market with insufficient evidence on added therapeutic value or evidence that suggests only a minor added therapeutic value, while industry sets prices for these medicines nevertheless at high level to cover R&D, production and other costs.[297,298] In such situations, it becomes difficult for payers to justify spending large amounts of their budgets on medicines that cannot show proven and significant added therapeutic value.

It should however be noted that for marketing authorisation purposes, a new medicine is and should not be required to be superior to medicines already authorised. This is because the effect of treatment in individual patients may differ and with greater choice of treatment, patients will have a better chance of finding a treatment most appropriate to their needs (see section 1 on the access chain). In other words, even if medicines are not superior to other medicines based on a direct, average comparison, those medicines can still offer important second or third line treatment options for individual patients.

2.3 Costplus-pricing

With costplus-pricing, the price of medicines is set by assessing production costs (incl. R&D costs, manufacturing, regulatory processes and compliance, overheads, operational costs) and adding a profit margin.[299] Although, in theory, this pricing policy is straightforward with clear and justifiable pricing rules that provide a level of certainty for budgetary planning and profits for the suppliers, it is not widely used for setting medicines prices at the ex-manufacturer or ex-wholesaler level. This may be partially due to the fact that it is currently difficult to implement because obtaining reliable cost information from suppliers is difficult.[300] Another, more fundamental reason may be that in a market economy, which is considered a crucial driver for investment and innovation, particularly valuable innovations yield higher returns than less valuable ones, rewarding the risk-taking investor for success in creating value.

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[295] Wieseler, B. et al. (2019) New drugs: where did we go wrong and what can we do better? BMJ 2019;366:l4340 doi: 10.1136/bmj.l4340

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

[297] Improving Access To Innovative Medicines Opinion by the Expert Panel on Effective Ways of Investing in Health (EXPH) factsheet_innovative_medicines_en_0.pdf (europa.eu)

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

[299] AIMs-fair-pricing-model-Accompanying-paper-to-the-fair-pricing-calculator_June2021.pdf (aim-mutual.org)

[300] World Health Organization. (2021). Cost-plus pricing for setting the price of pharmaceutical products: WHO guideline on country pharmaceutical pricing policies: a plain language summary. World Health Organization. https://apps.who.int/iris/handle/10665/341902. License: CC BY-NC-SA 3.0 IGO

There is a lack of transparency on research and development costs, often triggering criticism by policymakers and stakeholders.[301] The pharmaceutical industry estimates the research and development (R&D) costs for developing a medicine between US$2.2 billion and 2.9 billion. However, this figure is heavily contested by others. Irrespective, industry uses these figures to rationalise and justify the high prices charged for certain medicines.[302] Although companies' annual reports provide certain insights on overall R&D spending, companies do not do not disclose the relevant R&D costs spent on individual medicines brought onto the market. Either way, the market risks associated with R&D costs need to be put in perspective with the generated revenues.

Another point of concern is that the contribution of public funding to R&D costs is not known. By way of example, there is no clarity on the amounts of public funding spent on biomedical R&D in European countries. While the pharmaceutical industry claims that it has been paying for all costly clinical trials, this was contradicted by a study[303] financed by the Dutch government.

2.4 Managed entry agreements

A managed entry agreement (MEA) is a contractual arrangement between a manufacturer and health care payer/provider that enables access to (or reimbursement of) a novel medicinal product, subject to conditions. The objective of a MEA is twofold: to allow access to new high-priced medicines that would otherwise not be affordable, and to manage the uncertainty of limited evidence on clinical outcomes.[304] There are two basic categories of MEAs: finance-based (such as price–volume agreements) or performance-based (based on health outcomes).[305] Confidentiality is a major feature of all types of MEA. In some Member States, it is not even known which medicines are subject to an MEA, or which types of MEA are in use.[306] Experts agree that MEA are becoming more prevalent and could result in increasingly non-transparent prices "involving a mix of rebates across groups of medicines, discounts by indication, or based on volumes or expenditure caps, all of which mean it is complex to compute the final transaction price of a product."[307]

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[301] https://www.who.int/europe/publications/i/item/9789289058193

[302] Schipper, Irene & de Haan, Esther & Cowan, Roberta. (2019). Overpriced Drugs Developed with Dutch Public Funding.

[303] Schipper, Irene & de Haan, Esther & Cowan, Roberta. (2019). Overpriced Drugs Developed with Dutch Public Funding.

[304] Vogler S (2022): Payer policies to support innovation and access to medicines in the WHO European Region. Copenhagen: World Health Organization, Regional Office for Europe

[305]Medicines Reimbursement Policies in Europe. 2018. https://apps.who.int/iris/bitstream/handle/10665/342220/9789289053365-eng.pdf?sequence=1&isAllowed=y

[306] Pauwels K, Huys I, Vogler S, Casteels M, Simoens S. Managed entry agreements for oncology drugs: lessons from the European experience to inform the future. Front Pharmacol. 2017;8:171. doi:10.3389/fphar.2017.00171

[307] OECD Health Working paper 146. Exploring the consequences of greater price transparency on the dynamics of pharmaceutical markets. 2022. c9250e17-en.pdf (oecd-ilibrary.org)

2.5 Policies for generic and biosimilar competition

Member States have implemented a variety of pricing and reimbursement policy measures for off-patent medicines (including generic and biosimilar medicines) to promote competition, increase spending efficiency and contribute to access to innovation at affordable prices on patent expiry, and free up funds to be used for innovation.[308] Those include – but are not limited to – incentives for prescribing biosimilars and policies related to INN prescribing, switching by physicians and substitution by pharmacists. Acceptance and trust of biosimilar medicines by patients and health professionals is of utmost importance to enhance biosimilar uptake. There have been concerns by health professionals and patients as regards comparability of the biosimilar and originator, even though the available switching data does not indicate that switching from a reference product to a biosimilar is associated with any major efficacy, safety, or immunogenicity issues.[309,310] Recently, EMA and HMA published a joint statement to confirm the interchangeability of biosimilars to address this issue.[311]

Biosimilar competition

'Older' products (i.e. with expired protection period) are an important factor of pharmaceutical spending. Competition – generic and biosimilar – improves access and drives down prices. Due to the typically high prices charged for biological medicines, creating competition for their markets through the introduction of biosimilar versions can generate substantial cost savings[312]. In Germany, the waiting time for patients with rheumatoid arthritis to be treated with a biologic has been reduced from 7.4 years to 0.3 years after the introduction of biosimilars.[313] Looking at list price changes in markets with biosimilar competition, by 2020, biosimilars reduced the cost by almost 1/3.[314] One study estimated the impact of biosimilar entry in terms of healthcare systems savings between 2007 and 2020 for eight EU countries (France, Germany, Italy, Poland, Romania, Spain, Sweden, and the UK), ranging from €11.8 billion to €33.4 billion.[315]

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[308] Vogler S (2022): Payer policies to support innovation and access to medicines in the WHO European Region. Copenhagen: World Health Organization, Regional Office for Europe

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

[310] Barbier L, Ebbers HC, Declerck P, Simoens S, Vulto AG, Huys I. The Efficacy, Safety, and Immunogenicity of Switching Between Reference Biopharmaceuticals and Biosimilars: A Systematic Review. Clin Pharmacol Ther. 2020 Oct;108(4):734-755. doi: 10.1002/cpt.1836. Epub 2020 Apr 30. PMID: 32236956; PMCID: PMC7540323.

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

[312] Farfan-Portet M-I, Gerkens S, Lepage-Nefkens I, Vinck I, Hulstaert F. Are biosimilars the next tool to guarantee cost-containment for pharmaceutical expenditures? The European Journal of Health Economics. 2014;15: 223-8.

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

[314] IQVIA. The Impact of Biosimilar Competition in Europe. 2020. Available from: https://health.ec.europa.eu/system/files/2021-01/biosimilar_competition_en_0.pdf

[315] Haustein R, De Millas C, H er A, et al. Saving money in the European healthcare systems with biosimilars. Gabi Journal. 2012;1(3–4):120–126.

The importance of biosimilar competition has been growing since the first products entered the market in 2006. In 2020, biosimilar medicines accounted for 9% of the sales value of biological medicines in Europe. Nonetheless, uptake of biosimilars varies greatly across Europe. The share of sales of biosimilar medicines among all pharmaceutical sales in hospitals ranges from less than 2% in Bulgaria to 16.5% in Norway (the latter invested heavily in generating and disseminating evidence about safety of switching patients to biosimilar medicines). This variation may be partly explained by the range of different policies to encourage biosimilar uptake.[316]

2.6 Cross-country cooperation activities: regional joint negotiations or joint procurement

Several national governments have established cross-country collaboration initiatives on pricing, reimbursement and/or procurement to address the challenges to ensure access to high-priced medicines. The BeNeLuxA Initiative has concluded successful joint negotiations and further collaborates on horizon scanning, HTA, price and reimbursement negotiations and information sharing. The Nordic Pharmaceutical Forum and the Baltic Procurement Initiative have successfully concluded several joint tender processes for medicines and vaccines. Joint procurement is seen by some as a promising tool to help make small markets more attractive for suppliers, and therefore contributing to availability of medicines that would otherwise not be supplied.

2.7 Related EU cooperation activities

The decisions on the pricing and reimbursement of medicines are an exclusive competence of Member States (Article 168 TFEU). However, the Pharmaceutical Strategy points out that EU and national rules that do not directly regulate prices or reimbursement levels may also have a bearing on the affordability of medicines. In the implementation of the Strategy, the Commission has relaunched the cooperation between National Competent Authorities for Pricing and Reimbursement and the Healthcare Payers (NCAPR group). Through this group, the Commission supports mutual learning and best-practice exchange, including on pricing, payment and procurement policies. This work is based on voluntary and non-legislative actions.

ANNEX 11: SME

Micro and small businesses are an important sub-group driving innovation in medicines,317 particularly in sectors that are under-served due to technological challenges or lower expected market potential, such rare diseases.

The Agency has more than 1,900 EU-based SMEs registered in its corporate database (end 2020), and the European Confederation of Pharmaceutical Entrepreneurs

[316] Draft final report on the Study on Best Practices in the Public Procurement of Medicines (2022), not published.
[317] https://www.labiotech.eu/best-biotech/european-biotech-companies/.

(EUCOPE), which is Europe's principal trade body for small and mid-sized innovative companies working in the field of pharmaceuticals and medical technologies, has around 2,600 SME members

SMEs – and start-ups in particular – represent an important stepping-stone in the overall drug development space, providing a route for public science to push through discovery and pre-clinical research, moving through subsequent development phases and on to regulatory approval. SMEs have greater flexibility and lower costs and have an ability to signal potential to venture capitalists and launch IPOs in a way that is less easy for larger firms.

Pharmaceutical and biotechnology SMEs face additional market barriers as compared with their larger counterparts. The challenges are particularly significant given the very large cost, lengthy timelines and regulatory hurdles associated with the development of new medicines (e.g. 10 years from pre-clinical research through to regulatory approval with high attrition rates at each stage).

The EMA's engagement with SMEs has increased steadily since its set up its SME office in 2005 to provide advice and guidance, organise topical workshops and produces a dedicated newsletter for SMEs registered with EMA. The SMEs also have access to various fee incentives to support their medicine development programmes. The EMA annual report 2020 provides a series of data giving a sense of the scale – and trend – in SME engagement: the SME office received 222 requests for direct assistance on administrative or regulatory aspects and organised 10 briefing meetings to assist SMEs that were unfamiliar with the EU regulatory system. SMEs submitted 23 marketing authorisation applications, which is 19% of all applications received in 2020. Out of the 23 applications, 13 were for orphan-designated medicines. The CHMP gave a positive opinion for 16 medicines developed by SMEs. This is the highest number in the past five years and represents 18% of all positive opinions in 2020. Half of the medicines developed by SMEs (8) contained a new active substance.

Consultation of SME stakeholders

Given the nature of the SME community – large, diffuse with relatively limited time and capacity to engage with public policy – their direct participation in the consultation activities was limited. However SMEs were represented by the views of the European Confederation of Pharmaceutical Entrepreneurs (EUCOPE), which is Europe's principal trade body for small and mid-sized innovative companies working in the field of pharmaceuticals and medical technologies.

Impact.

When possible the impact on SMEs has been identified and described in the relevant sections of the document.

ANNEX 12 COHERENCE WITH THE REVISION OF THE GENERAL PHARMACEUTICAL LEGISLATION

The general EU pharmaceutical legislation regulates the way medicines (including medicines for rare diseases and children) are *authorised* across the EU and sets the framework in which they are marketed.

The Regulation on medicines for rare diseases is an 'add-on' to the general pharmaceutical legislation setting specific measures needed to address the market failure for medicines for rare diseases due to their small populations and potentially limited return on investment. The drivers for unmet medical need in the area of rare diseases remain relevant and therefore requires measures complementary to those provided by in the general pharmaceutical legislation.

Specialised legislation for rare diseases and children, entered into force in 2000 and 2007 respectively and currently being revised, complements the general EU pharmaceutical legislation to specifically support the development in these previously neglected areas, mainly through additional incentives and obligations.

The revision of the general pharmaceutical legislation and of the Regulations on medicines for rare diseases and for children are part of the same intervention aiming at achieving the same objectives set by the Pharmaceutical Strategy, including addressing unmet medical need of patients and access to medicines.

Unmet medical need / *high* unmet medical need

Both revisions will include a criteria-based definition on unmet medical need. The general pharmaceutical legislation will contain a definition for 'unmet medical needs' (UMN). The legislation on rare diseases will contain a definition of '*high* unmet medical needs' (HUMN), as in principle all orphan medicines will automatically satisfy the definition of UMN under the general rules; only a small subgroup of orphan medicines will qualify as 'HUMN'. The Commission has worked with Member States and the EMA and received input from stakeholders via consultations to develop criteria that can be introduced in the legislation. These criteria relate to disease level (whether the disease is life-threatening and/or seriously debilitating) and they relate to product level (whether there is another medicine or therapy already authorised and, if so, whether the treatment under development can satisfactorily cure the disease).

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

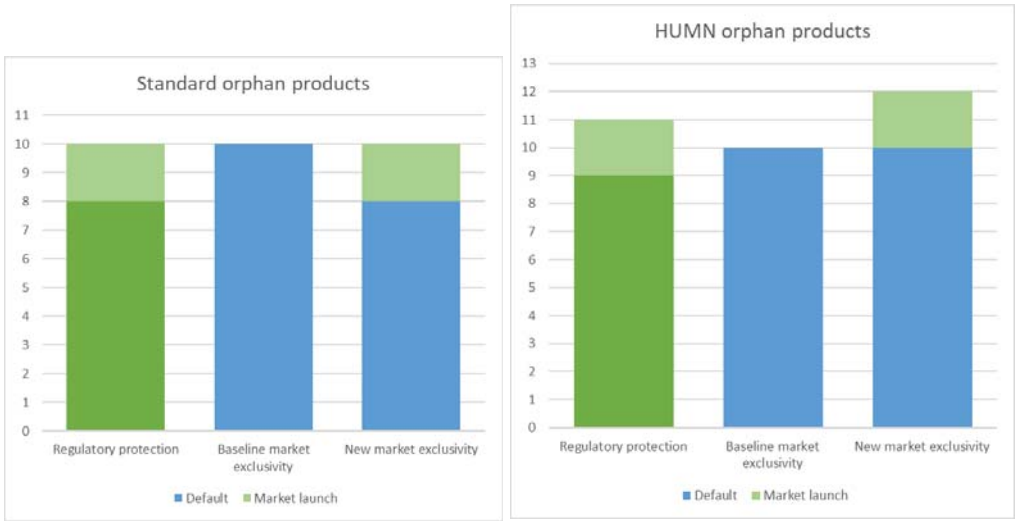
Both the revision of the general pharmaceutical legislation and the revision of the legislation for medicines for rare diseases and children adjust the system of incentives and depart from the 'one size fits all' approach to a 'modulated' one. Therefore, regulatory data protection for medicines and market exclusivity (in the case of orphan medicines) are modulated to reward companies developing medicines that deliver on needs of patients. Such needs are primarily reflected in the concepts of 'unmet medical need'.

The interplay between the regulatory protection and the orphan market exclusivity

(special protection for medicines for rare diseases) will be explained in detail in the revised impact assessment for the Regulations on medicines for rare diseases and for children. Essentially, the market exclusivity will be modulated in the same way as the regulatory protection, 2 or 1 years of the protection will be conditional to all EU market launch (depending which variation of the regulatory protection will be chosen by the legislator). For standard orphan medicines the market exclusivity will be equal to the regulatory protection (as today) and for medicines addressing high unmet medical needs, the market exclusivity will be one year more than the regulatory protection (these medicines will already enjoy a 1-year longer regulatory protection). Please note that the market exclusivity does not only protect from generic competition, but from similar products too (although this latter protection was rarely applied in the past).

The graph below demonstrates the interplay among the two protections for orphan medicines, with the 2-year market launch conditionality (Figure 26):

Figure 26 – interplay RDP and market exclusivity for standard and HUMN orphan products



Other points of coherence between the general and orphan medicines legislation are listed below. Together they create an integral system through:

- The revision of procedures for accelerated development and assessment of medicines for major public health needs taking into account novel technologies, in particular, the implementation of the PRIME scheme.
- Upstream cooperation among actors of the pharmaceutical lifecycle which foresees the reinforcement of mechanisms for cooperation and coordination between the regulatory authorities, Health Technology Assessment (HTA) authorities and payers building on the possibilities of the new HTA rules.
- Simplification of procedures and reduction of burden for generic/biosimilars. For example, currently it is not possible to apply for a marketing authorisation for a generic/biosimilar before the orphan market exclusivity period is over (i.e. 10 years after obtaining the marketing authorisation) whereas for other medicines this is possible when the data protection expires and before expiry of market protection. In the new system, application for marketing authorisation for generic

or biosimilar medicines will become possible *before* the expiry of market exclusivity.

- Future-proofing of the legislation, meaning its adaptation to rapid technological changes, including personalised medicine, will benefit patients as described in section 8. This will allow the full use of opportunities brought by gene therapies and personalised medicine which in many cases may concern medicines for rare diseases.

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

In fact, this different conclusion stems from the 'special' character of the antimicrobial sector and the particularity of the market failure in this case. Both cases relate to incentivising products for a limited number of patients (rarity of the disease in the first and desire to use the new antimicrobial as little as possible in the second). However, contrary to rare diseases, the societal risk of AMR (which potentially concerns the whole population and not just a few patients) and its actual and potential economic consequences combined with the very limited pipeline of antimicrobials with a new mechanism of action suggests that the advantage of having TEVs specifically for novel antimicrobials as an 'insurance policy' against resistant antimicrobials may surpass the disadvantages of the high costs for the very limited number of TEVs that are likely to enter the market.