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IMPACT ASSESSMENT REPORT

Accompanying the documents

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

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

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1 GLOSSARY

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

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

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

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

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

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

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

1 INTRODUCTION: POLITICAL AND LEGAL CONTEXT

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

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

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

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

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

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

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

[4] Idem.

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

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

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

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

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

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

[11] Pharmaceutical Strategy for Europe.

1.1 Legal context

1.1.1 General pharmaceutical legislation

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

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

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

1.1.2 Regulation on medicines for rare diseases

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

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

The Orphan Regulation establishes a two-step procedure:

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

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

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

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

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

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

1.1.3 Regulation on medicines for children

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

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

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

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

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

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

1.2 Political and policy context

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

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

1.2.1 Link with other initiatives

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

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

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

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

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

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

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

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

1.2.2 The pharmaceutical ecosystem

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

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

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

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

1.2.3 International context

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

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

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

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

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

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

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

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

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

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

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

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

1.2.5 COVID-19

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

2 PROBLEM DEFINITION

2.1 What are the problems?

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

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

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

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

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

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

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

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

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

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

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

2.1.2 Affordability of medicines is a challenge for health systems

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

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

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

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

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

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

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

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

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

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

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

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

2.1.3 Unequal access to medicines across the EU

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

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

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

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

2.1.4 The system caters insufficiently for innovation and creates unnecessary burden

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

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

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

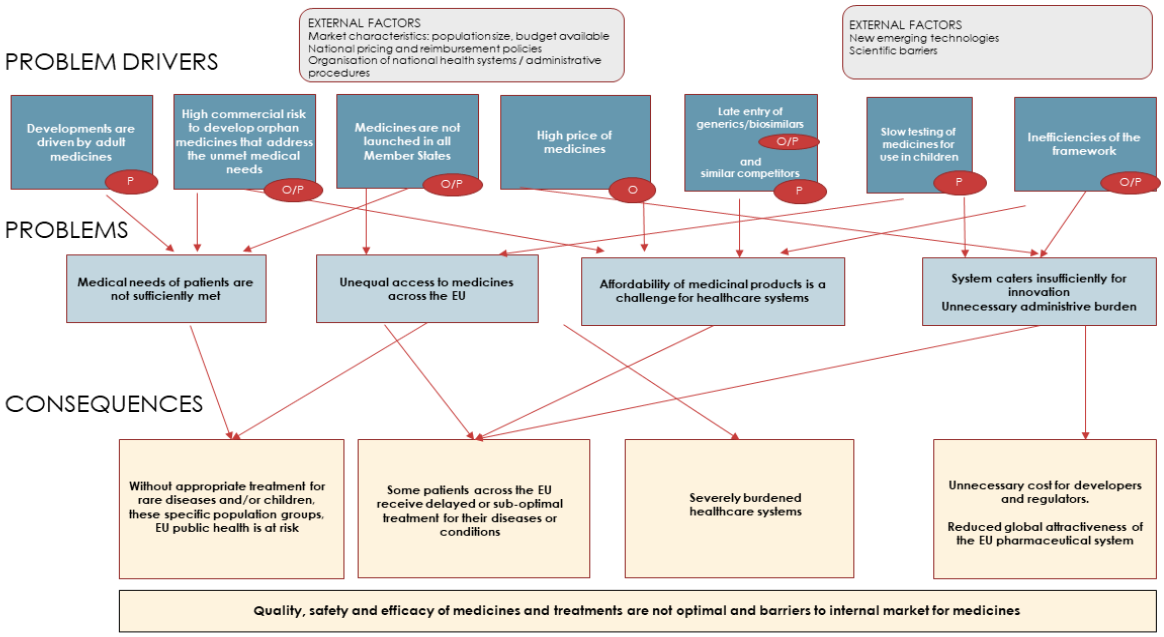
that are exclusive to adults. However, some of those medicines, in view of their mechanism of action[75], may be promising for the treatment of certain diseases in children and therefore should be researched further. This is often the case for anti-cancer medicines. Patient associations and healthcare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

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

2.2 What are the problem drivers?

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

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



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

2.2.1 Driver 1: Developments are driven by adult medicines

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

2.2.6 Driver 7: Inefficiencies in the legal framework

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

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

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

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

[101] Article 20 of the Paediatric Regulation.

[102] See also Section 2.1 of this SWD.

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

[104] Idem.

[105] Idem.

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

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

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

2.4 Megatrends

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

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

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[106] Section 6 of the Joint Evaluation.

[107] The EPSCO Council issued a recommendation in 2009 for Member States to create and adopt a plan focused on rare disorders by the end of 2013. Twenty-five Member States followed this recommendation.

[108] Twelve countries (Croatia, Czech Republic, Finland, France, Hungary, Latvia, Luxembourg, Portugal, Romania, Slovak Republic, Slovenia, Spain) have an ongoing national plan/strategy with a specified time-period. Austria, Belgium, Cyprus, Lithuania, and Germany have an 'open-ended' national plan/strategy. In seven countries, the national plan/strategy is expired: Bulgaria (expired in 2013), Denmark (apparently expired 2019), Estonia (expired in 2017), Greece (expired in 2012), Ireland (expired in 2018), Italy (expired in 2016), and the Netherlands (expired in 2018).

[109] Medicinal & plant protection products – single procedure for the granting of SPCs (europa.eu).

[110] The Megatrends Hub, https://knowledge4policy.ec.europa.eu/foresight/tool/megatrends-hub_en#explore.

[111] Foresight is the discipline of exploring, anticipating and shaping the future to help building and using collective intelligence in a structured, and systemic way to anticipate developments. Strategic foresight seeks to embed foresight into EU policy-making. See also: https://ec.europa.eu/info/strategy/strategic-planning/strategic-foresight_en.

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

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

3 WHY SHOULD THE EU ACT?

3.1 Legal basis

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

3.2 Subsidiarity: Necessity of EU action

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

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

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

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

3.3 Subsidiarity: Added value of EU action

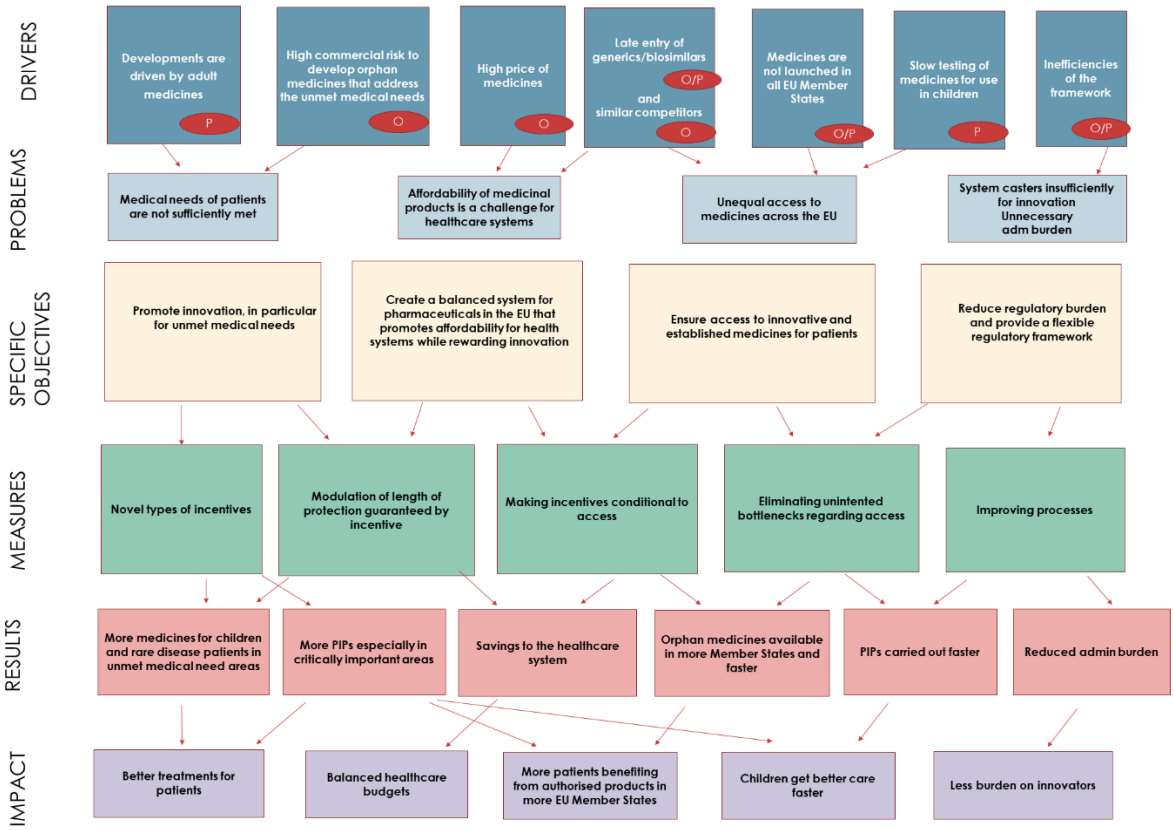
This initiative revises a system with recognised EU added value for the EU patients/citizens, pharmaceutical industry and medicines authorities leading to the authorisation of more medicines addressed to patients suffering from rare diseases and to children. It is expected to bring benefits by addressing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

4 OBJECTIVES: WHAT IS TO BE ACHIEVED?

4.1 General objectives

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

Table 2: Intervention logic



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

4.2 Specific objectives

The revision of the legislations will aim to:

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

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

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

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

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

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

4.2.4 Reduce the regulatory burden and provide a flexible regulatory framework

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

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

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[117] See also Section 2.1 of this SWD.

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

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

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

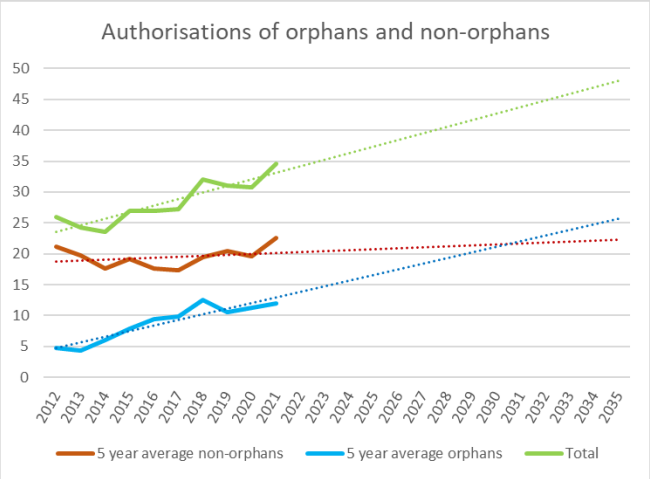
5 WHAT ARE THE AVAILABLE POLICY OPTIONS?

5.1 What is the baseline from which options are assessed?

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

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

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



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

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

[121] See also Section 6.1.1 of this SWD.

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

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

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[122] See also Section 2.1 of this SWD.

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

[124] See also Section 2.1 of this SWD.

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

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

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

5.2 Description of the policy options

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

5.2.1 Medicines for rare diseases

The following policy options have been assessed.

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

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

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

Elements common to all policy options

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

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

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

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

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

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

[134] Section 5.2.3 of the Joint Evaluation.

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

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

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

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

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

5.2.2 Medicines for children

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

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

Elements common to all policy options:

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

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

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

5.3 Options discarded at an early stage

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

6 WHAT ARE THE IMPACTS OF THE POLICY OPTIONS?

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

6.1 Medicines for rare diseases

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

6.1.1 Economic impacts of the policy options

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

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

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

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

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

Which medicines are affected by changes in market exclusivity?

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

Table 3: Length and type of protection of orphan medicines

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

Source: IQVIA

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

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

[150] See Section 1.2.4 of this SWD.

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

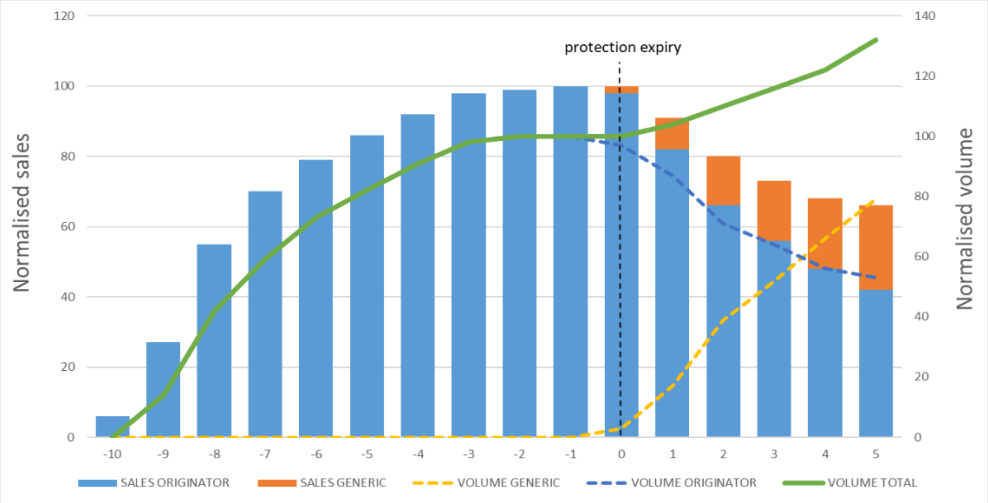
[152] Annual revenue of the medicine in its best-selling year over its lifetime (usually the last year before protection expiry).

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

How market exclusivity protection generates value/cost for stakeholders

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

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



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

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

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

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

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

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

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

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

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

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

.

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

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

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

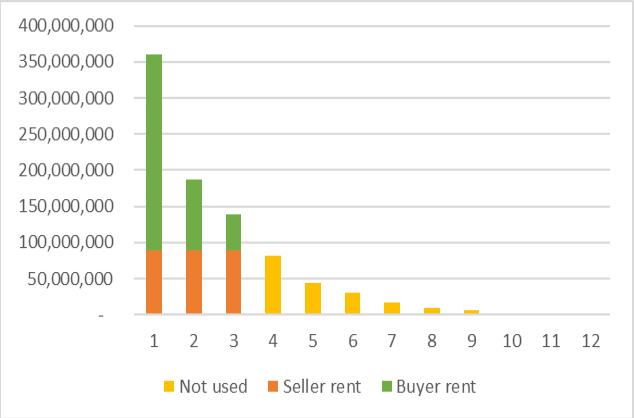
[155] Staff Working Document – Impact assessment on the general pharmaceutical legislation (Section 6).
[156] See also Annex 2: stakeholder consultation (synopsis report).
[157] As explained above under 'baseline scenario' in Section 6 of this SWD.

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

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

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

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



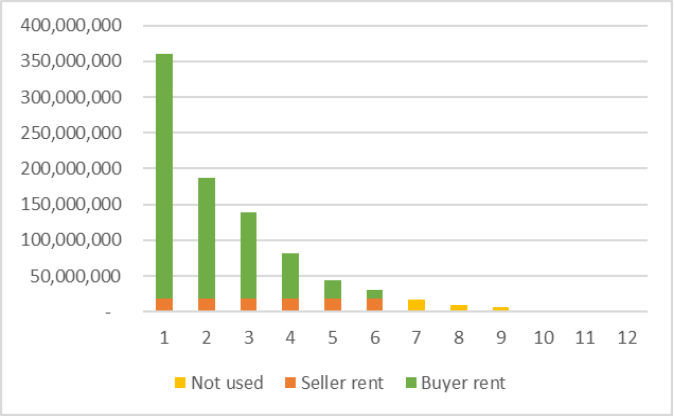


Table 5 – economic impact of the voucher	Systemic change (5 HUMN/year)
Gross profit of HUMN developer	**+€151m**
Gross profit of voucher buyers	+€576m

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

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

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

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

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

Option B – no market exclusivity

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

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

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

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

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

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

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

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

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

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

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

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

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

+1 year for HUMN addressing orphan medicines

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

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

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

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

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

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

Access conditionality

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

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

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

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

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

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

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

Well-established medicines

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

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

Stakeholder views

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

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

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

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

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

Impacts of the common elements to all options

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

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

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

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

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

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

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

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

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

6.1.2 Combined impact of the measures

Option A

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

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

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

[172] See also Section 5.2 of this SWD.
[173] The weighted average of protection for medicines with one or more additional indication
[174] Public payers' costs are under 'public authority' section; originators mean marketing authorisation holders of an original version of the medicinal products, as opposed to generic industry. Interests of those SMEs, which are involved in R&D of original products, correspond to interests of originators.

Common elements			
Day-1 entry of generic/biosimilars after ME expiry	€360m cost saving	-€354m gross profit	+€50m gross profit Predictable market entry
Abolishing 2-year ME extension for completing PIP	€96m cost saving legal clarity	-€94m gross profit	+€13m gross profit
Global marketing exclusivity	cost neutral, more predictable	Shorter protection time Stronger protection =cost neutral	cost neutral, more predictable
Total balance	**+€538m extra cost** +1-2 additional HUMN medicines per year **Lower access**	**+€279m gross profit** **Unfair and inefficient distribution of profits**	**-€59m gross profit**

Conduct of business: The additional reward in the form of a transferable exclusivity voucher will increase the profits of industry (originators including SMEs), although disproportionately for the voucher *buyers* rather than for the HUMN developers in view of the potential high number of vouchers. It is therefore not expected to have positive impacts on HUMN developments. Moreover, keeping the same length of market exclusivity for all orphan medicines, which is detached from their investment costs and level of innovation addressed, may lead to overcompensation of some pharmaceutical companies. Introducing increased scientific support for HUMN would be positive for business engaged in areas of more risky research (often SMEs). All the measures aimed at the faster generic/biosimilars competition[175] are expected to have a positive effect for generic industry. As these measures are aimed to avoid unjustified benefits being drawn from the market exclusivity, the overall impact on the conduct of business would be positive.

Other common element measures aimed at improving patients' access (transfer to another company rather than withdrawing an orphan medicine; capping the duration of the orphan designation at 7 years) will be of limited effect for businesses. Still, the transfer of an orphan medicine, facilitated by publishing the intention of withdrawal, could have a positive impact on the conduct of business.

Providing for the possibility to adapt the current definition of an orphan condition to ensure that the legislation is 'fit' to embrace technological and scientific advances would have a positive impact on businesses. Removing the orphan designation criterion of return on investment will have no impact on businesses since it has never been used[176] (although it will simplify the system). Transfer of responsibility for adopting decisions on 'orphan designations' from the Commission to the Agency will create a faster decision-making and, therefore, a positive impact on conduct of business. **SMEs:** as SMEs are involved mostly in early stage of R&D and invest in riskier areas of R&D targeting innovative products, transferrable exclusivity vouchers could potentially increase the value of their research assets/authorised product once sold to big pharma, however due to the high number of vouchers, such a positive impact would be diluted.

[175] Generics/biosimilars can enter the market at day-1 of the expiry of the exclusivity period; Reduction of consecutive periods of market exclusivity for new indications of the same orphan medicine by introducing them under the same "Global Marketing Authorisation" (GMA); the market exclusivity granted to a second generation product that is similar to the first generation product shall not be applied in respect of generic products of the first reference product for which the market exclusivity expired.
[176] Section 5.1 of the Joint Evaluation.

Public authorities: The introduction of a voucher may carry a significant cost to the national authorities as longer exclusivity periods will delay entry of cheaper generics.

Impacts on R&D / innovation: The additional incentives will support increased return on investment for developers and bring additional investment into R&D for HUMN. However, in the case of vouchers a more limited impact is expected as due to the potential high number of vouchers, their value will diminish.

Administrative burden: Procedural simplifications will reduce administrative burden.

Internal market: The impact on the internal market can mainly be seen from the viewpoint of the number of new products on the market, their availability and patient's access across the EU. The new incentives would increase the number and availability of new orphan medicines. On the other hand, lack of specific measures to achieve EU-wide market launch and patient access would retain the level of fragmentation of the internal market as in the baseline. Delayed generic entry would hinder competition, and keep prices high for a longer period compared to the baseline.

Competitiveness/trade: The special incentives for HUMN, including the transferable voucher, and common measures for simplification are expected to improve competitiveness and attractiveness of the EU pharmaceutical sector, especially SMEs, and support increased investment in medicine development to address unmet medical needs.

Digital impact: Measures that are being considered in the revision of the general pharmaceutical legislation (for example the digitalisation of procedures and the possibility to analyse real world data) are expected to support pharmaceutical companies and public authorities to enjoy the benefits coming from digital innovation in the sector. The European Health Data Space[177] will provide a common framework across Member States for the access to high-quality real world health data and will be particularly relevant for small patient populations. The data, for example collected through rare disease registries, will become accessible and are expected to allow progress in research and development of medicines and provide new tools in pharmacovigilance.

Option B

The combined impact of the measures is shown below in Figure 5, depicting the cost-benefits of Option B on all stakeholders.

Figure 5 – cost/benefits for all stakeholders of Option B

	Cost/benefit for **public payer and patients**	Cost/benefit for **originators**	Cost/benefit for **generic industry**
Option specific measures			
No market exclusivity	+€725m cost savings Political signal to divest rare disease R&D likely 1-2 HUMN less per year	-€751m gross profit	+€101m gross profit
Common elements			
Day-1 entry of generic/biosimilars after ME expiry	€360m cost saving	-€354m gross profit	+€50m gross profit Predictable market entry

[177] COM(2022) 197 final.

Abolishing 2-year ME extension for completing PIP	€96m cost saving legal clarity	-€94m gross profit	+€13m gross profit
Global marketing exclusivity	cost neutral, more predictable	Shorter protection time Stronger protection =cost neutral	cost neutral, more predictable
Total balance	**€1.181m cost saving** **1-2 HUMN less medicines per year** **0% increase in access**	**-€1.199m gross profit**	**+€164m gross profit**

Conduct of business: Absence of market exclusivity is expected to result in less R&D in medicines for rare diseases, as originators will not have an incentive to engage in such R&D. Generic entries will gain faster access to the market, however, there will be also a smaller number of new original products, which could offset to some extent this gain. The impact of common elements in this option is similar as for Option A. **SMEs:** No market exclusivity will particularly negatively impact SMEs involved in R&D as they will face a high risk that no big company will be eager to buy the result of their R&D if this incentive is abolished. In consequence, they may find it too economically risky to engage in R&D of orphan products.

Public authorities: Health payers may benefit from lower average costs for medicines due to earlier generic entry. The extent of these benefits will depend on originators' response to the absence of the reward, and it is possible that average prices will be adjusted upwards to some degree to offset the elimination of the compensation mechanism. However, these savings for public authorities should also be seen in the perspective of costs related to the lack of adequate treatments (see also the following subchapter under 'social impacts of the policy options').

Impacts on R&D / innovation: The absence of a reward in the form of market exclusivity may lead to the reprioritisation of research in the area of orphan products and, hence, negatively affect investment into R&D neutralising the positive effects of the common elements for the development of new products in particular in areas of HUMN.

Administrative burden: Simplification of procedures (common elements) is expected to bring positive results.

Digital impact: The digital impact in this option is similar as for Option A.

Internal market: Earlier generic entry due to the elimination of the reward may in theory improve access, but any gains for the internal market may be offset by the absence or belated availability of new orphan products aimed at areas of HUMN and innovative orphan products.

Competitiveness/trade: Elimination of the market exclusivity could weaken the global competiveness of EU based originators compared with the current situation, which is not expected to be outbalanced by positive aspects of procedural simplifications from the common elements.

Option C

The combined impact of the measures is shown below in Figure 6, depicting the cost-benefits of Option C on all stakeholders.

Figure 6 – cost/benefits for all stakeholders of Option C

	Cost/benefit for **public payer and patients**	Cost/benefit for **originators**	Cost/benefit for **generic industry**
Option specific measures			
+1 year of ME for HUMN addressing medicines	+€82m additional cost 1-2 additional HUMN medicines per year	+€94m gross profit	- €13m gross profit
1 year of ME conditional for full EU launch	€288m cost saving from non-complying medicines (6 non-complying MP) Broader and faster access to complying medicines	-€282m gross profit loss (6 non-complying MP) +€4m additional cost (4 complying MP)	+€38m gross profit gain due to non-complying medicines (6 non-complying MP)
Common elements			
Day-1 entry of generic/biosimilars after ME expiry	€360m cost saving	-€354m gross profit loss	+€50m gross profit Predictable market entry
Abolishing 2-year ME extension for completing PIP	€96m cost saving legal clarity	-€94m gross profit loss	+€13m gross profit
Global marketing exclusivity	cost neutral, more predictable	Shorter protection time Stronger protection =cost neutral	cost neutral, more predictable
Total balance	**€662m cost saving** **+1-2 additional HUMN** **+9% broader and faster access**	**-€640m gross profit loss**	**+€88m gross profit**

Conduct of business: The modulation of market exclusivity duration is expected to target those areas where research is mostly needed and where the investments are most risky, therefore would contribute to a fairer distribution of incentives. The impact of common elements in this option is similar to Option A.

SMEs: The 10-year market exclusivity for products addressing HUMN and innovative products will benefit SMEs (active in riskier R&D). Although the 10-year market exclusivity period corresponds to the current baseline, by the fact that market exclusivity periods will be differentiated, the relative value of HUMN/innovative products will increase. As to the common elements, their costs are expected to be the same across all the options (for details see Option A).

Public authorities: The costs to national health systems are expected to increase, as compared to the baseline, due to an increase of the maximum market exclusivity periods (10 years + 1 year for the market launch in the whole EU + max. 2 years for new indications) and thus delayed entry of generics. The reduced (compared to the baseline) 5-year market exclusivity period, as applicable to products with well-established use, is not expected to result in major significant reduction of costs to public authorities costs.

Impacts on R&D / innovation: Additional ME, given for orphan products which address HUMN and innovative products will boost R&D in those areas.

Administrative burden: The impact of administrative costs is similar as for Option A, i.e. less administrative burden is expected, thanks to procedural simplifications. Some additional documentation may be required for eligibility for the HUMN category, and hence for additional ME.

Digital impact: The digital impact in this option is similar as for Option A.

Internal market: The effect on the internal market (availability and patient access) is expected to be positive due to an additional ME period for EU-wide launch as well as access-inducing measures from the common elements.

Competitiveness/trade: The system of modulated ME is expected to boost competitiveness and attractiveness of the EU pharmaceutical sector and support increased investment in orphan medicines development. The common elements such as procedural simplification are expected to have a further positive effect.

6.1.3 Social impacts of the policy options

The revision of the orphan regulation aims to meet two *societal* needs:

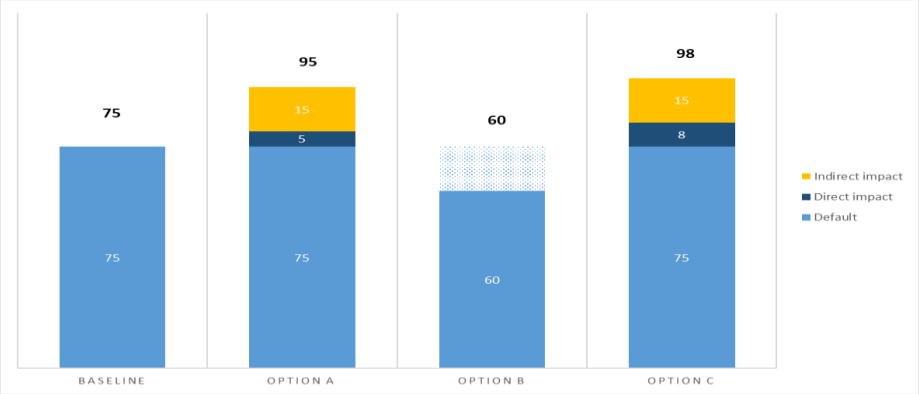
- Increase therapeutic options for rare disease patients, especially in disease areas where therapies do not exist or are insufficiently effective (high unmet medical needs - HUMN).
- Ensure better and equal patient access to medicines for rare disease across the EU.

Therefore, we measure the social impacts by two indicators: 1. Number of medicines addressing HUMN and 2. The increase in patient access.

Medicines addressing HUMN

Orphan medicines addressing HUMN can be considered more valuable to society than other new medicines, because of the lack of any existing alternative and the existing burden for patients and health systems. This does not undermine the value of development of medicines for other rare diseases as the existence of more than one therapeutic options benefit patients, health care professionals and increase competition. Figure 7 below summarises the expected change in number of medicines addressing HUMN under the different options[178].

Figure 7 - Expected number of HUMN addressing orphans in the various policy options.



Option A maintains the baseline incentives and adds the vouchers on top of it for HUMN products. It could stimulate extra investment in HUMN products. The downside of the vouchers is that it may

[178] Apart from the social impact of Options A/B/C, there is also the common element to all options of the **adaptation of the current definition of an orphan condition** to ensure that the legislation is better 'fit' to embrace technological and scientific advances. This will support the development of products in HUMN areas (and should also cater for more efficient procedures for designation and authorisation).

become a very expensive and inefficient way of rewarding developers. We estimate that compared to the baseline (75 HUMN for 15 years), the **overall number of HUMN products could go up to 80** with the additional incentive (direct impact).

Option B is not only indifferent to HUMN medicines, but it abolishes the market exclusivity, sending a negative signal to orphan medicine developers targeting the European market, namely that orphan medicines are not anymore a priority in the pharmaceutical legislation. This signal would likely trickle down to research funders, investors and national authorities, resulting in a decline in orphan medicines, and consequently a decline in HUMN medicines too. **An estimated 20% decline in newly authorised orphan medicines** would bring down the number of **HUMN addressing orphans to 60** in the next 15 years.

Option C offers a modulation of market exclusivity period, favouring medicines addressing HUMN and rewarding them with 1-year additional protection. This translates into a 14% higher protected revenue, or 7.7% higher gross-profits compared to other medicines, making their development and authorisation more rewarding commercially. Overall, the incentive could directly **increase the number of HUMN addressing medicines by 10%, to 83** in the next 15 years (*direct* impact).

We can expect that both **Option A** and **C** will also have important *indirect* impacts. An EU level definition of HUMN under the common elements could lead to important spill-over effects, just as it happened with the introduction of the orphan designation in the EU Orphan Regulation in 2000[179].

All these spill-over effects led to a successful market creation that boosts investment and innovation. A definition of HUMN would therefore allow labelling research and medicinal products that have highest utility for society, and channel public resources – either research funding or favourable P&R conditions – towards them. The extra benefit given for HUMN in the orphan regulation would showcase the EU's commitment, and invite other actors to follow suit in their own realms.

Improving access to orphan medicines

The revision of the *general* pharma legislation proposes a solution where 1 year of additional regulatory protection would be granted in case the medicine is launched in all EU countries within 2 years from authorisation. According to the analysis conducted in the impact assessment of the general pharmaceutical legislation[180], this not only would increase the number of Member States with access (and thus the percentage of the EU population covered), but the medicine would also be made available for more people in a significantly shorter time than in the baseline.

Option A by keeping the market exclusivity at 10 years without any modulation, would nullify the access conditionality introduced in the general pharma legislation. Option A would therefore equal the current status quo (baseline).

Option B, which abolishes market exclusivity, would leave the protection period defined only by the general pharma for orphan medicines. The general pharma legislation will incentivise access, and it is worthwhile for companies to make an effort to launch in all Member States. Option B should result in higher and faster access than the baseline.

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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

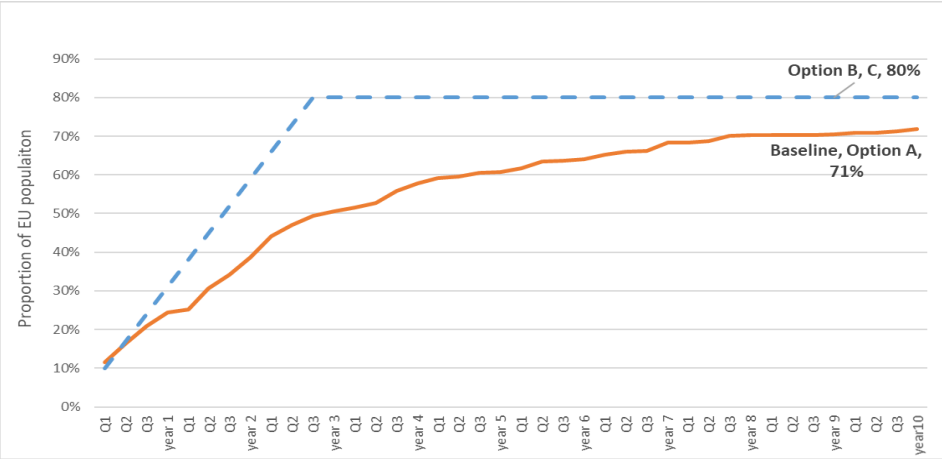


Figure 8 demonstrates the expected impacts of the various policy options on patient access[181]. Option B and C reach a higher plateau of 80% EU population covered, and also much faster than Option A/baseline, two years following authorisation.

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.

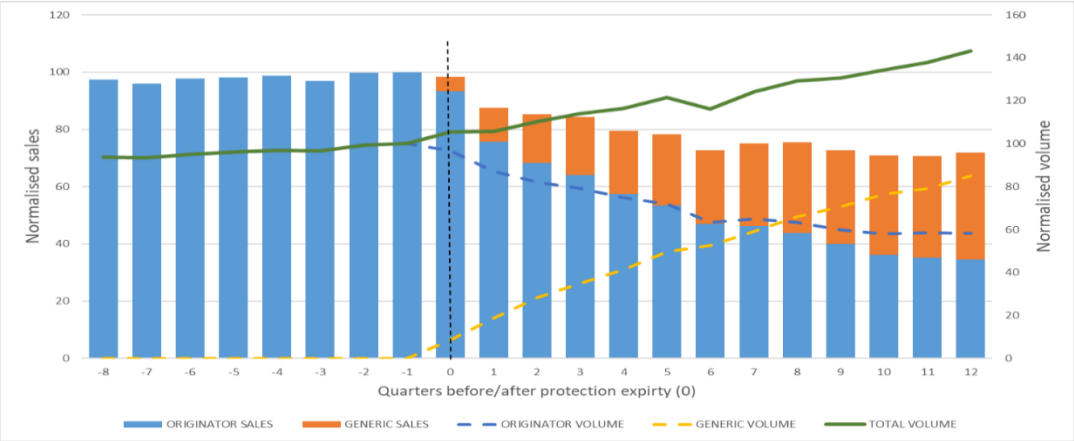
How the SPC extension generates value/cost for stakeholders

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.

[191] These criteria will identify products addressing HUMN that will subsequently profit from longer or more generous regulatory incentives under the various options.

These measures are intended to embrace scientific advances and provide more effective and efficient processes and procedures.

7.1.2 Efficiency

Table 17 - Overall comparison of the policy options for orphan products in terms of efficiency

Efficiency: comparison of benefits and costs	**Baseline**	**Policy Option A**	**Policy Option B**	**Policy Option C**
Overall costs and benefits	0	+/-	+/-	++
Administrative costs	0	+	+	+
Impact on SMEs	0	+	-	+

Estimated impact compared to the baseline: + + positive, + moderately positive, –/+ neutral, – moderately negative, – – negative and – – strongly negative

As regards the savings and benefits of the various options, **Option A** is the most expensive for health systems/patients due to the introduction of a novel incentive (regulatory data protection vouchers) and the most generous for pharmaceutical industry due to the same novel incentive. It leads to an overall €538m of extra yearly costs to public payers, while generating €279m of extra profits for originators (and a yearly loss of €59m for generic industry[192]). **Option B** creates savings to health systems/patients, but fails to deliver substantial benefits on access and on rewarding pharmaceutical industry for innovation (including HUMN products). It leads to an overall €1.181m of yearly cost savings for public payers/patients, to a yearly loss of €1.199m profits for originators, and profits of €164m for generic industry[193]. **Option C** is the most **cost-efficient**. It will bring some savings to the health systems compared to the baseline (together with the measures to foster faster generic/biosimilar completion under the common elements). At the same time it also brings the most *benefits* in terms of patient access and the development of products addressing HUMN. In monetary terms, the overall impact is €662m of yearly cost savings to public payers/patients, 640m of profit loss to originators and 88m of profit gains for the generic industry.

As regards **administrative costs**, the impacts for companies are expected to derive mostly from the common elements. Savings will come from streamlined procedures for the designation and authorisation of orphan medicines, scrapping the orphan designation criterion on the basis of insufficient return on investment and transferring the responsibility for adopting decisions on orphan designations to the Agency. Concerning the impact **on SMEs**, all **options** are expected to have a positive impact thanks to the common elements and the (additional or graduated) incentives especially for the development of products addressing HUMN (**Options A** and **C**). On the contrary, the abolition of the market exclusivity (**Option B**) is expected to have a negative impact on SMEs as they may find it more difficult and less rewarding to start the development of orphan medicinal products.

7.1.3 Coherence

Table 18 - Overall comparison of the policy options for orphan products in terms of coherence

Criteria	**Baseline**	**Policy Option A**	**Policy Option B**	**Policy Option C**
Coherence	0	+	+/-	+

Estimated impact compared to the baseline + means that the assessment is positive, and – means that it is negative

[192] See Section 6.1.2 for the combined (monetary) impact of the policy options including cost-benefit tables for all stakeholders per option.
[193] Idem.

In terms of **coherence**, all policy options were assessed with regards to their external and internal coherence. As regards the *external* coherence, the interaction of the Orphan Regulation with other EU legislative acts[194] was assessed and its interaction with national plans and strategies. All the three options were considered to be externally coherent. Furthermore, it was also explored how the policy options align with related measures taken at national level by Member States[195]. In relation to these national measures, it was found that significant heterogeneity exists in the state of advancement of national policies, plans, or strategies for rare diseases[196].

Internal coherence mostly related to the interaction with the revision of the general pharmaceutical legislation. Options A and C are internally coherent with this revision as the market exclusivity is kept or modulated under these options whereas Option B is not coherent (due to the elimination of the market exclusivity). Furthermore, all three policy options are internally coherent with the revision of the general pharmaceutical legislation[197].

The current overall system of regulatory procedures and incentives provided by the general pharmaceutical and specific orphan legislation has been considered as 'working in a coherent way' on the basis of the perceived effect by stakeholders interviewed[198]. Furthermore all options are expected to be coherent with external activities and contribute to the achievement of SDG 3 ("health and well-being") and SDG 9 ("innovation and infrastructure").

7.2 Medicines for children

7.2.1 Effectiveness

Table 19 - Comparison of policy options in term of effectiveness – medicines for children

Criteria	Baseline	Policy Option A	Policy Option B	Policy Option C
Effectiveness: contributing to achieving the policy objectives				
Objective 1: Foster investment in research and development of medicines for children	0	+	-	+
in particular for unmet medical needs	0	++	-	+
Objective 2: Create a balanced system for pharmaceuticals in the EU that promotes affordability for health systems while rewarding innovation	0	--	+	+
Objective 3: Increase patient access to medicines for children	0	+	-	+
Objective 4: Streamline processes and reduce administrative burden	0	-	+	+
Effectiveness: other impacts Social impact				
Timely completion of PIPs	0	+	-	+
Number of completed PIPs	0-	+	-	+

Estimated impact compared to the baseline: + + positive, + moderately positive, 0 neutral, – moderately negative, – – negative and – – strongly negative

[194] Regulation (EU) 2018/781 on similarity; Regulation (EC) No 2141/96 on the examination of an application for the transfer of a marketing authorization for a medicinal product; Regulation (EC) No 2141/96 on application for the transfer of a marketing authorization; Council Regulation (EC) No 297/95 on fees.
[195] Nearly all the Member States have adopted a national plan or strategy for rare diseases as of October 2021, except Malta and Sweden.
[196] No data was found to further explore the link between these national plans and the proposed options.
[197] For instance, they both provide a definition for (H)UMNs and create links between specific research priorities and the provision of incentives; they both push for innovations reaching the market more quickly through timely approval and the introduction of an access conditionality; they both simplify regulatory and administrative procedures.
[198] See also Annex 2: Stakeholder consultation (synopsis report).

On objective 1, **Option A** performs best. Thanks to the introduction of novel incentives for products addressing the UMN of children, in parallel to the 6 months SPC extensions for all paediatric products, together with the effect resulting from certain common elements (for example, the waiver system which takes into account the mechanism of action of a product and a better support for early development of UMN products) is expected to results in the highest number of products developed in particular in areas of UMN. At the opposite, **Option B** is expected to result in a decrease of products as the removal of the reward for the completion of the PIP may discourage in particular small companies or academics to start research and development in areas which could be beneficial for children. **Option C**, is expected to result in an increased number of products including addressing UMN of children compared to the baseline, thanks to the action of certain common elements. However to a lower extent than option A, as the reward for products completing a PIP will remain unchanged (6 months SPC extension).

As regards **objective 2**. The affordability of medicines for children depends from the corresponding adult medicines. However, any modification of the length of the paediatric SPC extension, which covers not only the "paediatric" medicine but also the "adult" part of a product , would have an impact on the timing of the generic entry and consequently on affordability. The introduction of additional rewards for products addressing UMN of children in **Option A**, is expected to result in a delayed generic entry for these products and therefore result in the highest impact for the health systems. **Option B** is expected to create savings for health systems compared to the baseline due to the abolition of the reward for the completion of a PIP resulting in an early generic entry. However, it will not ensure that children will be able to benefit of this improved affordability as often generic products do not cover specific paediatric preparations, dosages, pharmaceutical forms. The originator product remains the only available source even after the expiry of the protection period. While the price of originator decrease following generic entry, the lack of competition for certain paediatric formulations and preparations cannot guarantee that affordability will be achieved for medicine for children. **Option C** is expected to result in small improvement for what concern affordability compared to the baseline, thanks to common elements which by reducing the costs related to a PIP (for example by introducing early support for products addressing UMN or simplifying and streamlining the PIP process,) may results in lower prices of the product.

Regarding **objective 3**, the streamlining and simplification of the PIP system and the capping of delays under which PIP have to be completed are expected to result in a faster conclusion of the PIP and indirectly to a faster access for patients for **Options A and C**. In **Option B**, the removal of the rewards for the completion of the PIPs, is expected to counter the positive effect of the common elements as companies may de prioritise paediatric research and development. This may result in longer waiting times for children to get medicines adapted to their needs.

On **objective 4**, the reduction of administrative burden for all options analysed derive from the common elements (simplified and evolutionary PIP). In addition, for **Option A** the introduction of a supplementary reward in term of a voucher or of a supplementary extension of the SPC for UMN product may increase the overall administrative burden for companies and for public authorities. In the case of transferrable voucher, a system to manage the vouchers issues will need to be put in place and companies would be expected to fulfil further administrative requirements compared to the baseline situation. In the case of an extension of the SPC extension for products addressing UMN, in particular generic companies may face further complexity to plan the launch of generic medicines due to the further complexity that will be added to the SPC system.

Social impact: As mentioned in section 6.2.3, benefits for children derive from the avoidance of ADRs and increased quality of life thanks to medicines studied and authorised for specifically for them. However, as the average impact of ADR is relatively mild, even if potentially may result in a thalidomide-like scenario, and it is not possible to anticipate which products will be developed, it is not possible to provide a direct quantitative assessment of these benefits. The social impact is therefore related to the number of new paediatric products developed and to their timely access to patients due to a quicker completion of the necessary paediatric studies. The impact of the options

on the number of medicines for children has already been described under objective 1 above. Concerning the timely completion of PIPs both **Option A** and **Option C**, thanks to the common elements (cap of deferrals and simplification and streamlining of the PIP procedure) are expected to increase a faster completion of the PIP compared to the baseline, resulting to a quicker availability of products dedicated to children. In **Option B**, the removal of the reward for the completions of the PIPs, is expected to counter the positive effects of the common elements as certain companies my no more prioritise studies in children, resulting in later completion of the PIP and less products specifically developed for children.

7.2.2 Efficiency

Table 20 - Comparison of policy options in term of Efficiency – medicines for children

Criteria	**Baseline**	**Policy Option A**	**Policy Option B**	**Policy Option C**
Efficiency				
Overall costs and benefits	0	-	+	0
Administrative costs	0	-	+	+
Impact on SMEs	0	+	-	+

Estimated impact compared to the baseline: + + positive, + moderately positive, 0 neutral, – moderately negative, – – negative and – – strongly negative

Concerning saving and benefits, **Option A** gets the lowest scoring. The introduction of increased rewards for products addressing UMN of children would – on the one side - benefit economically the originator industry (441m gross benefit). On the other side, this would create also much higher costs compared to the baseline for health systems and patients (307 m). At the Opposite, **Option B,** abolishing the reward for the completion of PIPs is the one which is expected to score higher bringing benefits for patients and health systems (1510 m of savings) despite the higher costs for industry (in particular for originators -1756m) which will continue to be obliged to conduct PIP (even more than in the baseline due for example to the introduction of the mechanism of action in the common elements) without receiving any reward for this obligation. **Option C** for what concerns the saving and benefits originating from the paediatric SPC extension is expected to remain overall neutral compared to the baseline as the SPC paediatric extension will remain as in the baseline, the only difference in cost benefits for public authorities and industry will be related to the increased number of PIP and products that are expected to be developed as a consequence of the common elements.

Concerning administrative costs, the impact is expected to come from the common elements so all options are expected to score equality positive in this respect. Nevertheless, the novel rewards intended to be introduced under **Option A** are expected to increase the overall administrative costs for companies and for public authorities.

Concerning the impact on SMEs, **Option A and C** are expected to have a positive impact thanks to the common elements and the rewards granted for the conduction of paediatric studies. The abolition of the rewards on **option B** is expected to have a negative impact in particular on SMEs who may find more difficult to start paediatric development project due to abolishment of financial rewards for conducting clinical studies in children.

7.2.3 Coherence

Table 21 - Coherence

Criteria	**Baseline**	Policy Option A	Policy Option B	Policy Option C
Coherence	0	-	**-**	+

Estimated impact compared to the baseline + means that the assessment is positive, and – means that it is negative

In terms of *external* coherence the policy options have been assessed against the following initiatives: the SPC Regulation, the clinical trial Regulation, the HTA Regulation, national funding initiatives. Concerning the SPC Regulation, Option A and C, which maintain the SPC paediatric reward, are coherent with Regulation and its ongoing revision. The simplifications and reduction of administrative burden that the SPC revision will bring will be complementary to the ones that will be achieved by the simplification and streamlining of the PIP procedure. The **EU Clinical Trials Regulation**[199] facilitates the conduct of trials in small populations scattered in several MS. Therefore supporting measures of Option A and C in their intent to foster the development of new products in particular in areas of UMN. Option B, with the abolition of the SPC paediatric extension and the possible de prioritisation of clinical research in children by companies, may counter the positive effect expected from the clinical trial Regulation. The HTA Regulation, which is expected to overcome the national HTA procedures diversity, and to reduce their length and complexity in different Member States, is expected to be coherent with all the options

The coherence with the revision of the general pharmaceutical legislation has also been assessed. All the options proposed are coherent with the preferred option selected in the revision of the general pharmaceutical legislation and the two initiatives share similar objectives. In the case of transferable exclusivity vouchers (TEVs) foreseen in Option A, at first glance, there may seem to be incoherence between the two regimes. As in this impact assessment TEVs are considered as an ineffective incentive to generate innovation, whereas in the case of antimicrobials in the general pharmaceutical legislation, they may be a plausible incentive if applied strictly. This different conclusion stems from the 'special' character of the antimicrobial sector and the risk of a high number of TEVs if applied for paediatric medicines. The societal risk of AMR (which potentially concerns the whole population and not just a few patients) and its actual and potential economic consequences combined with the very limited development pipeline of antimicrobials suggests that the advantage of having TEVs specifically for novel antimicrobials may surpass the disadvantages of the high costs for the very limited number of TEVs that are likely to enter the market.

All policy options contribute to SDG 3 ("health/well-being") and SDG 9 ("innovation/infrastructure").

7.3 EU added value and proportionality and subsidiarity

All options for both initiatives bring EU added value for health systems/patients and pharmaceutical industry. All options for both initiatives are consistent with the EU's right to act under the Treaty of the Functioning of the EU (covering public health protection, the single market and the free movement of products within the EU). All options propose actions that will allow the objectives of the revision to be achieved to a greater extent than if Member States were acting alone. Furthermore, all options are proportionate in the sense that they do not go beyond what is necessary to achieve the objectives.

All options pursue the objectives of the revision and provide a clear demarcation between EU and Member State level actions. They do not propose any change to the national health care systems which are in the exclusive power of Member States (Article 168 TFEU), but the measures are expected to facilitate the development of medicines for rare diseases and children.

7.4 Limitations of the comparison

For both legislations quantification has not been possible for several indicators. Therefore qualitative analysis have been conducted. There is also a level of uncertainty in the findings described in this chapter owing to the influence of other contextual factors such as developments in the

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

pharmaceutical sector, other relevant legislations (e.g. HTA Regulation, SPC Regulation) and policies at Member State level (e.g. for pricing and reimbursement). Further details are provided in Annex 4 section 3.c.

8 PREFERRED OPTION

8.1 Orphan medicinal products

The preferred option is **Option C**. This option is expected to provide a balanced positive outcome contributing to the achievement of the four objectives of the revision. It is expected to increase the number of orphan medicines compared to the baseline. It will especially refocus investments in products addressing HUMN, without undermining the development of medicines for rare diseases where treatments already exist but where new therapeutic options can still benefit patients and healthcare providers. This will boost research and innovation and would also improve the competitiveness of the EU industry including SMEs. Option C provides a balanced market exclusivity system, also allowing for earlier market entry of (similar) competitor orphan medicines while incentivising products in areas of HUMN. Options C leads to the best results in terms of patient access, due to the proposed access conditionality for the extension of the market exclusivity. The streamlining and the simplification of the procedures (better coordination between scientific committees, transferring the responsibility for orphan designation to the Agency) is expected to result in more efficient procedures and timely authorisation. Furthermore, more flexible criteria to better define an orphan condition will make the authorisation procedures more 'fit' to accommodate new technologies and reduce administrative burdens. The introduction of a Global Marketing Authorisation should also lead to a simplification of the system.

Table 22 - Yearly costs and benefit calculated per interested stakeholder group for preferred Option compared to the baseline

	Cost/benefit for **public payer and patients**	Cost/benefit for **originators**	Cost/benefit for **generic industry**
Option specific measures			
+1 year of ME for HUMN addressing medicines	+€82m additional cost 1-2 additional HUMN medicines per year	+€94m gross profit	- €13m gross profit
1 year of ME conditional for full EU launch	€288m cost saving from non-complying medicines (6 non-complying MP) Broader and faster access to complying medicines	-€282m gross profit loss (6 non-complying MP) +€4m additional cost (4 complying MP)	+€38m gross profit gain due to non-complying medicines (6 non-complying MP)
Common elements			
Day-1 entry of generic/biosimilars after ME expiry	€360m cost saving	-€354m gross profit loss	+€50m gross profit Predictable market entry
Abolishing 2-year ME extension for completing PIP	€96m cost saving legal clarity	-€94m gross profit loss	+€13m gross profit
Global marketing exclusivity	cost neutral, more predictable	Shorter protection time Stronger protection =cost neutral	cost neutral, more predictable
Total balance	**€662m cost saving** **+1-2 additional HUMN** **+9% broader and faster access**	**-€640m gross profit loss**	**+€88m gross profit**

The impact of preferred **Option C** will be complemented by elements of the preferred option and common elements in the revision of the *general* pharmaceutical legislation. In particular:

- The access conditionality, linking 1 year of additional regulatory data protection with effective placing on the market and supply of medicines in all Member States, within 2 years from authorisation, is aligned with the access conditionality of 1 year of additional market exclusivity for medicines for rare diseases. The positive effect on access and availability is expected to be even stronger for innovative and HUMN orphan medicines for which extended market exclusivity and regulatory data protection will be combined.
- Procedures will be simplified and streamlined. Provisions to streamline assessment activities between committees, and pre- and post-authorisation procedures, such as efficient interaction between different legal frameworks (e.g. medical devices) and downstream decision makers (HTA bodies, payers), abolishing renewals, integrating digital tools and real world evidence into the regulatory system and IT-driven processes (e.g. electronic submissions and variations of marketing authorisations) are some of the measures that are expected to reduce burdens and costs for companies and public authorities.

The legal instrument used is planned to continue to be a Regulation.

Competitiveness and future of innovation under reduced market exclusivity

Industry stakeholders claim that the reduction of market exclusivity period would harm future innovation and EU competitiveness. The incentives are agnostic to the geographic origin of the medicines, therefore the reduction would not harm EU companies more than non-EU companies coming to the European market (non-EU companies develop 80% of new medicines introduced to the EU market).

However, lower profits may transform into less innovation at a global scale. Option C estimates a total loss of €640m in gross profits. Industry re-invests on average 25% of their gross profit into R&D, consequently €160m may be lost for innovation. In 2021 the global pharmaceutical industry has invested €230b in R&D, hence the potential loss amounts to 0.07% of global R&D investment. If we wanted to translate this into medicines, only 1 in the next 1500 new medicines would not be developed because of the reduction, a likely invisible loss over the next 15 years.

Taken together with changes proposed in the general pharmaceutical legislation[200], and to the paediatric incentives, the combined effect remains marginal compared to global R&D investments.

8.2 Paediatric medicinal products

The preferred option resulting from the analysis presented in Chapter 7 is **Option C**. This option is expected provide a positive outcome contributing to all the objectives of the revision and results balanced under all the criteria screened.

Option C is expected to yield to an increased number of products in particular in areas of UMN needs of children which are expected to reach children faster than today while ensuring a fair return of investment for medicines developers who fulfil the legal obligation to study medicines in children, as well as reduced administrative costs linked to the procedures that follow from the obligation. The increased costs for public authorities and corresponding benefits for originators correspond to the expected development of more products addressing in particular UMN of children.

All stakeholder groups consulted support option C[201].

[200] The preferred option of the revision of the general pharmaceutical regulation has two variations, depending on the eventual length of the market launch incentive. One variation results in +€298m gross profit, and the other results in -€602m gross profit for the innovator industry.

	Cost/benefit for **public payer and patients**	Cost/benefit for **originators**	Cost/benefit for **generic industry**
Option specific measures			
Maintaining current extension	Cost neutral	Cost neutral	Cost neutral
Common elements			
Mechanism of action	3 more PIPs +€151m cost (1 SPC extension)	+€169m gross profit +€66m cost	-€33m gross profit
Cap in the maximum length of the deferrals	Faster completion of PIPs Cost neutral	Cost neutral	Cost neutral
Total balance	**+€151m cost** **+3 PIP** **+earlier access**	**+€103m gross profit**	**-€33m gross profit**

The positive impact of the preferred option will be complemented by some of the elements of the revision of the *general* pharmaceutical legislation. In particular

- The criteria to identify UMN to be defined in the general pharmaceutical legislation will be the same for medicines for children. Therefore medicines for children identified as addressing UMN will be entitled to any eventual additional regulatory incentives that could be granted to products addressing UMN. It is estimated that such provision will give an additional push to developers. Moreover, the additional regulatory incentives to be provided for products addressing UMN will serve as a "safety net" for a fair return on investment in cases when the SPC reward may not cover all Member States or may be not available (historically, around 50% of the completed PIPs benefitted from the SPC reward).
- Provisions linking regulatory data protection incentives with the effective placing on the market and supply of products medicines in all Member States, within a certain period of time, will also apply to medicines for children. This will further improve patient access to these medicines across the EU.
- Marketing authorisation procedures will be streamlined. This may decrease life-cycle costs for paediatric medicines and may help to ensure that originators maintain paediatric formulations over the entire life-cycle of the adult product and may increase the probability that generic companies copying the adult product will include the paediatric version[202].

The legal instrument used is planned to continue to be a Regulation.

8.3 REFIT (simplification and improved efficiency)

Preferred option orphans: The transfer of the responsibility for orphan designations from the Commission to the Agency is expected to result in simplification and increased efficiency. Furthermore, the abolishment of the yearly reporting for companies on the status of development of their orphan designation will entail less administrative burden. Better coordination between scientific committees will lead to faster assessment of the marketing authorisation application and lower the administrative burden for industry and reduce the number of interactions with the Agency.

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[201] In the public and targeted consultations, industry criticised the introduction of the mechanism of action as a common elements. However, they now support the measure as it brings alignment between the European and the US regulatory system: https://www.efpia.eu/about-medicines/development-of-medicines/regulations-safety-supply/stimulating-the-development-of-new-medicines-for-children/

[202] There is no obligation for generics and biosimilars to adapt their products to children friendly forms

Preferred option paediatrics: Streamlining and simplification of procedures for agreeing a PIP are expected to lower the administrative burden for industry. This is due to the reduced number of interactions with the Agency during the PIP process and to the simplified dossier that will be requited in certain cases. Industry strongly supports the simplification and streamlining of the PIP procedure.

8.4 Application of the 'one in, one out' approach

Orphan medicines: Reduction of the administrative costs for companies (about 3,6 m € per year) will result from preparing slightly fewer applications for an orphan designation and taking away annual reporting requirements. Pharmaceutical companies including SMEs, whose products are designated as orphan medicinal products, will continue to pay *reduced* fees for regulatory activities including for the marketing authorisation[203]. The implementation of the common elements will result in savings. Some of these savings will be offset by a slight increase in administrative costs for pharmaceutical industry due to the creation of a seven-year temporal validity for an orphan designation to stimulate timely product development and application for a marketing authorisation and the variable duration of market exclusivity for eligible products.

Paediatric medicines: A reduction of the administrative costs for companies per PIP will results from the simplification of the PIP procedure and from the new evolutionary PIP system. This streamlined process could affect up to 25-30 % of the procedures. There would be an increased effort for the Agency's Paediatric Committee (+ 10-20 %), but a reduced burden for industry (30%) due also to a better alignment with the US system.

Moreover, a less demanding PIP in the case of the paediatric only products will reduce burden and timing of the PIP preparation and application, including for PUMA products. However, specific impact figures cannot be provided as the number of paediatric only products cannot be anticipated.

An increase of the number of PIP and products is expected under the preferred Options and this has to be factored in the overall yearly administrative costs. The preferred option is therefore expected to result in a yearly reduction of administrative costs of 1,50 m €. Details are provided in Annex 3.

9 HOW WILL ACTUAL IMPACTS BE MONITORED AND EVALUATED

A series of monitoring parameters have been identified to evaluate the impact of the proposed measures on each of the objectives.

Table 23 - Proposed monitoring parameters

SPECIFIC OBJECTIVE	MEASURES OF SUCCESS AND RESPECTIVE MONITORING INDICATORS		DATA SOURCES
1. Promote innovation, in particular for unmet medical needs.	Pipeline of innovative new medicines for rare diseases and children.	• Number of orphan designations including for HUMN • Number of medicinal products for rare diseases and for children authorised • Number of medicinal products for rare diseases and for children authorised to address H/UMN of these populations • Number of PIP agreed on the base of the mechanism of action of the products • Number of PIP addressing UMN • number of pre-marketing regulatory support (scientific advice, PRIME, rolling review) • Number of research program financed by the EU concerning paediatric products addressing UMN	EMA data Data collected from EU research programs
Create a more balanced and competitive system	-Decreased costs for the healthcare	• Number of generic/biosimilar marketing authorisations.	OECD data; DG SANTE Country

[203] Orphan incentives | European Medicines Agency (europa.eu).

that keeps medicines affordable for health systems and patients while rewarding innovation.	system deriving from orphan products). -Faster introduction of generic and biosimilar medicines in Member States.	• Level of pharmaceutical spending per Member State for orphan medicines.	Health Profiles.
Ensure access to innovative and established medicines for patients.	-Timely access for medicines for rare diseases and children accessible in more Member States.	• Time to market in the various Member States of medicines for rare diseases • Time necessary for the completion of every PIP • Number of PIP finalised after the authorisation of the corresponding adult product and delay of the authorisation of the paediatric indication.	International HTA Database INAHTA, EMA data; IQVIA sales data; EMA data
Reduce the regulatory burden and provide a flexible regulatory framework.	-Reduction of approval time for orphan medicines. -Reduction of the time necessary to complete a PIP.	• Number of simplified PIPs agreed • Number of evolutionary PIPs agreed and conducted • Number of innovative study designs, orphan designations • Number of modifications per PIP • Average completion time of PIPs • Change in percentage of authorisation requests of orphan products granted	EMA data

All the data supporting the indicators are already collected at EMA level. They would not result in any additional administrative burden Annual reports on medicines for children are already published by the Commission could be adapted to accommodate the data mentioned above.

While some indicators (like the number of PIPs agreed or the number of orphan designated products) may provide some preliminary trends, only the number and type of medicines authorised will be able to provide a realistic picture if the objectives of the revision have been achieved. Therefore, it should be taken into account that the development of medicines is a long process and the completion of a clinical development plan can take up to 10-15 years. Incentives and rewards exert their effect up to 10 years after the marketing authorisation and the benefit for patients needs to be measured over a period of time of at least 5-10 years after a medicines is authorised.

ANNEX 1: PROCEDURAL INFORMATION

Lead DG, Decide Planning/CWP references

The Directorate for Health and Food Safety (DG SANTE) is the lead DG on the initiative on the Revision of the EU legislation on medicines for children and rare diseases.

The initiative is in the European Commission's Work Programme for 2022, in Annex II: REFIT initiatives, under the heading 'Promoting our European Way of Life'. The initiative has received the validation in the Agenda Planning on the 1 September 2020 (reference PLAN/2020/6688), and the Inception Impact Assessment was published on 24 November 2020.

Organisation and timing

An Inter-Service Steering Group was set up and included the Secretariat-General) Legal Service, BUDG (Budget), RTD (Research and Innovation), COMP (Competition), TRADE, GROW (Internal Market, Industry, Entrepreneurship and SMEs) and the JRC (Join Research Centre). It met 5 times from 30 October 2020 until 18 May 2022.

Consultation of the RSB

A first version of this Impact Assessment Report was submitted to the RSB on 30 May 2022, the meeting took place on 22 June 2022 and the RSB written (negative) opinion was received on 24 June 2022. After the first submission, the Board concluded the following:

1) The coherence and interaction with the general pharmaceutical legislation (and its revision) and other initiatives is not clear.
2) The presented narrative and intervention logic do not clearly describe and link the problems, objectives, proposed measures and their impacts, particularly in the area of availability and accessibility of these medicines.
3) The description and impact analysis of the options is unclear and their costs and benefits are neither well-presented nor compared. Given the apparent small differences between the impacts of the different options, the report does not sufficiently discuss the sensitivity of the impact analysis and how this uncertainty affects the conclusions.

The table below lists the changes in response to the recommendations of the RSB in its first opinion. Besides these modifications, targeted corrections and amendments have been included to address the technical comments provided by the RSB to DG SANTE.

Recommendation of the RSB	Modification in the impact assessment report in response to the Board's recommendations
(1) The report should clarify the links and overlaps with the general pharmaceutical legislation and its upcoming revision. It should be clear how the ambition of the general pharmaceutical legislation is included in this initiative and how the objectives and measures of the two initiatives create synergies and/or trade-offs. The link with other initiatives should be integrated better in the report, e.g. regarding cooperation at global level. Specific research programmes for these medicines and their link to the general development of medicines should be outlined. Based on a clearer problem identification, the report should present a more coherent narrative with clarified specific objectives and better linked measures. It should	Links with the general pharmaceutical legislation and explanations about the interplay have been included throughout the whole document. In particular, the intervention logic and Sections 5 (options) and 6 (impacts) have been amended. The options have been simplified (see also Annex 5 for a full overview of the options) in order to better allow their assessment and comparison and methodology has been aligned to better show the links with the revision of the general pharmaceutical legislation in order to be able to better take into account the impact of that revision on this SWD. This has allowed to better explain the ambitions of the initiatives, synergies and trade-offs that can be gained. Annex 8 has been introduced and further

better explain the enabling framework character of the initiative and that overall progress depends heavily on the effective interplay with other critical measures. This should help to better manage the expectations of the present initiative.	explains the overview of the overall legal pharmaceutical framework and related legal instruments like the SPC regulation. Relevant research programmes have been further outlined. Their link with the development of medicines has been further elaborated in Section 1.3.1 and Annex 8. The problem definition has been streamlined, a detailed problem tree has been added in the report. A full-fletched intervention logic has been added, better showing links between objectives and measures. The enabling framework character of both initiatives (general pharmaceutical revision and revision of the Regulations on medicines for rare diseases and children) have been made clearer, especially in Sections 1.3 and 2.1. The interplay with other critical measures, in particular those outside the competence of the EU and within the competences of Member States (pricing & reimbursement, for instance) has been further explained in Sections 2.1.2 and 2.1.3.
(2) The problems of availability and accessibility of these medicines should be clarified, together with their drivers, substantiated with robust evidence (e.g. EC pharmaceutical sector inquiry), and informed by the views of affected stakeholders. The report should be clear if the problems mainly lie with the Member States or the market behaviour of pharmaceutical industry or result from an economic market failure (e.g. lack of economic incentives). It should also be clear on the relative importance (and possible interaction) of the drivers and at which level these can be tackled most effectively while respecting subsidiarity and Member States competences. Finally, it should be clear what the different specific objectives are regarding availability and accessibility, how they relate to each other, and what the trade-offs are (e.g. higher absolute number of new medicines vs number of patients benefitting from new or less costly medicines).	The problems description has been clarified (see also point 1). The problems related to patient access have been further elaborated and substantiated in Sections 2.1 and 2.2 and have been informed by the views of affected stakeholders. It has also been made clearer what is in the EU's remit and what belongs to the Member States. It has been clarified how the different options and common elements aim to tackle issues concerning development on medicines and access to medicines by patients. The links between the specific objectives have been better outlined.
(3) The description of the options should be clarified, both in content and how the specific measures work together to tackle the problem drivers and reach the specific objectives. The effectiveness of the different measures in tackling the problem drivers and delivering on the specific objectives should be better assessed.	The options have been simplified and their functioning has been adjusted and clarified in Section 5. It has been further elaborated how the common elements work together with the options and how they aim to contribute to the achievement of the different objectives. It has also been assessed how the different policy

The report should clearly demonstrate that the proposed measures are complementary and compatible with the upcoming revision of the general pharmaceutical legislation.	options in tackling the problems and contributing to the achievement of the objectives including in relation to the pharmaceutical incentives under the general pharmaceutical legislation (in Sections 6 and 7). This to also calculate the cumulative effects of those two revisions. The complementarity of the two revisions has been demonstrated by reference to their common objectives (Section 2.2.) and by taking into account the impacts of the options of the general pharmaceutical legislation (Section 5).
(4) The analysis of the impacts should be structured better and presented clearly. The analysis should be understandable for a non-expert reader with cross references between results and calculations. The assumptions should be outlined clearly. The impacts on SMEs should be analysed further and the evidence available for assessing these impacts should be put forward. The report should be clear which measures are most cost-effective.	We have aligned the methodology used for the analysis of the assessment of the impacts (Section 6 and Annex 4) with the methodology used for the impact assessment of the *general* pharma legislation, with the aim to improve clarity, readability and consistency. The assumptions on which the model was based have been further explained and impacts on SMEs have been analysed, where possible. The available evidence on the impacts on SMEs has been presented in Section 6 and Annex 11 (SME test).
(5) The comparison of options should be supported by a clear overview of costs and benefits of the different options and a clear assessment in terms of effectiveness, efficiency and coherence. This should help the selection of a preferred option and in assessing its proportionality. The trade-offs for the different options regarding innovation, availability and affordability should be described, including possible unintended consequences such as earlier or later entering in the market of both innovative as well as generic medical products. Given the apparent small differences between the impacts of the different options, the report should better reflect the sensitivity of the impact analysis to the limitations of data and the modelling assumptions and how this uncertainty may affect the conclusions regarding the preferred options.	Chapter 7 has been improved to present independently and in a more extensive form the comparison of the options under the angles of effectiveness, efficiency and coherence. The trade-offs have also been described while comparing the options. The consequences (trade-offs) of the different options regarding innovation, patient access and affordability have been better described. The different options have been simplified and better described with a stronger focus on the monetary impacts per stakeholder with more significant results per option (avoiding small differences between the impacts).
(6) The report should present more systematically the views of different stakeholder categories on the problems, options and their impacts.	The views of different stakeholders have been systemically presented throughout the various Sections of the report.

A revised version of the Impact Assessment Report was submitted to the RSB on 28 October 2022 for a final opinion. The table below lists the changes in response to the recommendations of the RSB.

Recommendations of the RSB	**Modifications in the impact assessment report in response to these recommendations**
The report does not sufficiently assess the impacts of reduced regulatory protection periods on the sectors' capacity to finance future medicine innovation and international competitiveness.	A dedicated subsection on competitiveness and future innovation is added to section 8.1, on p. 67.
The report lacks clarity regarding safeguards for market access measures.	Section 5.2.1., description of policy options for rare diseases have been complemented, and explanation on the safeguards (and reference to the revision of the general pharmaceutical legislation) has been added to option C on page 32.
Some of the impact analyses are not sufficiently developed.	Several improvements have been introduced in the text: • Price differences and data accuracy – section 2.2.4 on p. 24 • A footnote explains the difference between scientific advice and Horizon Europe funding – section 5.2.2. p. 34 • An explanation on direct and indirect impacts of HUMN incentive is provided in Annex 4 (methodology) – section 3.d p. 104 • More details are added on how the percentage of population served over time is estimated for the options in Annex 4 (methodology) – section 6., p. 113 • An explanation on the concept of economic rent regarding the voucher is provided – section 6.1.1. p. 35 • Access gain is quantified in Figure 6 (p. 49) and Table 22 (p. 67)

Evidence, sources and quality

The Impact Assessment has built on the:

- Joint Evaluation of the Paediatric and Orphan Regulations (published in 2020)[204]

- Participatory workshops bringing stakeholders together to discuss various topics (see Annex 2: Stakeholder Consultation).

[204] https://ec.europa.eu/health/system/files/2020-08/orphan-regulation_eval_swd_2020-163_part-1_0.pdf

- The findings of the study on the economic impact of the supplementary protection certificates, pharmaceutical incentives and rewards in Europe[205].

Extensive stakeholder consultation was organised, with inputs gathered through a public consultation, targeted surveys, an interview programme and a focus group (for more information, see Annex 2: Stakeholder Consultation).

Evidence on costs of research and development was particularly difficult to gather. Public authorities and pharmaceutical companies provided only few responses to the costing survey. Data from published literature was also used.

[205] Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe (2018): https://ec.europa.eu/health/sites/health/files/human-use/docs/pharmaceuticals_incentives_study_en.pdf.

ANNEX 2: STAKEHOLDER CONSULTATION (SYNOPSIS REPORT)

a. Introduction

This report provides an overview of the consultation activities carried out in the context of the *Impact Assessment of the revision of the EU legislation on medicines for children and rare diseases*, the stakeholders and their opinions. These activities are:

- The public consultation (PC), from 7 May to 30 July 2021.
- Targeted surveys, including Options survey and Costing survey both for pharmaceutical companies and public authorities, from 21 June to 30 July 2021 (late responses were accepted until the end of September 2021, due to the summer period).
- Interview programme, at the end of June 2021.
- Focus groups, on 23 February 2022.

The following five key stakeholder groups (identified as priority groups by the EC) were targeted, namely:

1. Public authorities (European Medicines Agency (EMA), national competent authorities incl. ministries of health, health technology assessment (HTA) bodies, 'payers') in particular on topics such as rewards and incentives, regulatory procedures and efficiency, access, pricing and reimbursement.
2. Pharmaceutical companies (including small and medium-sized enterprises (SMEs)) in particular on their experience with paediatric investigation plans (PIPs), incentives and rewards, product development, as well as marketing authorisations.
3. Civil society representatives (e.g., patients, public health organisations) in particular on issues surrounding accessibility and availability, as well as unmet medical needs (UMN) and QALYs.
4. Healthcare providers (e.g., professional associations) in particular on the adoption of mechanism of action (MoA) criteria as well as questions relating to access and availability.
5. Academia/researchers/research organisations in particular on their involvement in clinical and pre-clinical research, scientific development, as well as the concerns linked to defining the current research priorities.

The consultation actions were agreed with the Inter-Service Steering Group in May and July 2021 and have been carried out as planned.

i. Public Consultation

The questionnaire of the PC[206], which was published on the Commission's *Have Your Say website*,[207] was made available in 23 official EU languages. A list of shortcomings identified in the Evaluation of the EU legislation on medicines for children and rare diseases was presented to the PC respondents. These included: (1) insufficient development in areas of the greatest needs for patients; (2) unequal availability, delayed access, and often unaffordable treatments for patients in the EU Member States (MS); (3) inadequate measures to adopt scientific and technological developments in

[206] Link to the OPC: https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12767-Revision-of-the-EU-legislation-on-medicines-for-children-and-rare-diseases/public-consultation_en.

[207] The published initiative 'Medicines for children & rare diseases – updated rules' on the Have your say website is available at https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12767-Medicines-for-children-&-rare-diseases-updated-rules_en .

the areas of paediatric and rare diseases and (4) procedures which are insufficient and burdensome. In view of this, citizens and stakeholders were invited to share their **views and experiences on the main obstacles** they face concerning treatments for rare diseases and children, on **possible ways to overcome** these obstacles, and **how to future proof the current legislation**.

In total, the PC received 305 responses, 87 of which came from non-governmental organisations, 67 from EU citizens, 39 from company/business organisations, 33 from academia/research institutions, 32 from business associations, 12 from public authorities, four from non-EU citizens, two from consumer organisations, and one from a trade union. As to the representation of SMEs, 12 stakeholders were micro, small and medium-sized companies/business organisations, from eight different Member States.

The remaining 28 responses have been submitted by 'other' stakeholder groups. Overall, 88.8 % of responses came from the EU MS, 3.6 from the US, while 7.8 % came from other countries.

In total, five separate contributions were submitted as part of the consultation activities. This includes position papers by APME (Association of Pharmaceutical Manufactures in Estonia) and Medicines for Europe, Novo Nordisk letter to the European Commission, and RECLIP's (Spanish Paediatric Clinical Trials Network) position on the proposed options.

It should be noted that multiple responses among different respondents that were either exactly the same or very similar were found. For instance, such responses were based on the official position of organisations such as EPFIA, EUCOPE and SIOPE.

ii. Targeted surveys

Options Survey

The Options Survey consisted of targeted questionnaires and was designed to engage with the EU-level and national public authorities, pharmaceutical industry representatives (including SMEs), civil society representatives (e.g., paediatric and rare disease patient organisations), healthcare providers and academia to gather detailed information on their views and preferences on the policy options as well as the costs of developing and marketing specific medicinal products.

In total, the Options Survey received 124 responses. Overall, public authorities were the most represented stakeholder group among the Options Survey respondents (46 %). Among public authorities, the representatives of EMA provided the most responses, followed by national agencies, the European Reference Networks (ERNs), health ministries, public health organisations, and national HTA agencies. Healthcare providers also provided a sizeable number (24 %) of responses. Among these were individual healthcare professionals, healthcare organisations, and one professional association. Academia was also relatively well-represented among the respondents (12 %). Fewer responses came from the pharmaceutical industry (9 %) and civil society (9 %).

Costing Surveys

Two types of Costing Surveys were designed: the *Costing survey for pharmaceutical companies* and the *Costing survey for public authorities*.

The **Costing Survey for pharmaceutical companies** consisted of a *questionnaire* to marketing authorisation holders of paediatric and orphan medicines. The questionnaires aimed at obtaining precise figures on administrative, research and development (R&D), manufacturing and marketing costs incurred specifically in relation to the development of paediatric and orphan medicines to inform the Cost-Benefit Analysis.

Only three responses were received to the Costing Survey from the pharmaceutical industry, namely three multinational pharmaceutical companies based in Europe or US. However, since none of them provided the requested cost elements, only a general qualitative description of the costs incurred, they were deemed insufficient for further analysis. Alternative strategies for the collection of relevant data have been identified, including through the analysis of the data from published

literature (mainly the SWD of the Joint Evaluation and Neez, et al. ("Estimated impact of EU Orphan Regulation on incentives for innovation." - Dolon Report 2020).

The **Costing Survey for public authorities** targeted the representatives of the national competent authorities and health ministries. The questionnaire was aimed at obtaining precise figures on the costs, including staff costs, costs of research subsidies distributed by national authorities, and costs of fee waivers and protocol assistance provided by the EMA. These data fed directly into the CBA.

Seven responses were received to the **Costing survey for public authorities**. These responses primarily contained quantitative information about the costs incurred by the same authorities; therefore, they fed directly into the CBA, and they will not be analysed in the Synopsis Report.

iii. Interview programme

The key goal of the interview programme was to collect in-depth information from the most relevant representatives from the five stakeholder groups on certain elements of different policy options as well as on their economic, social and environmental impacts.

60 interviews were conducted: the **majority (42 %) were with public authorities, 28 % were with the pharmaceutical industry, 13 % with academia, and 12 % with civil society representatives.** The least represented group, due to a low response rate, was the **healthcare providers making up 5 % of stakeholders** in the interview programme.

iv. Focus group

The purpose of the focus group dedicated to **potential changes in the current system of regulatory incentives foreseen under the Paediatric and Orphan Regulations** was to validate the key assumptions about the expected impact of a selection of changes. Five key stakeholder groups participated: civil society, healthcare providers, academia, pharmaceutical industry, and public authorities. The focus group hosted **78 participants**. The most represented groups among participants were **public authorities and civil society**, while a similar share of participants represented healthcare providers, academia and pharmaceutical industry[208]. In terms of public authorities, there were representatives from 17 different EEA countries[209].

Methodological approach

The relevant principles and steps on stakeholder consultations outlined in the Commission's *Better Regulation Guidelines* were followed in designing the consultation strategy. The stakeholder consultation's main steps included designing the consultation strategy, conducting consultation work, and informing policymaking through the preparation of the reports.

As with the PC, the data for targeted surveys was cleaned, where relevant, identical responses and campaigns were identified[210]. While for the targeted surveys, most questions helped to obtain quantitative data, the PC, interviews and focus group primarily gathered qualitative data.

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[208] The options given to the participants were: civil society, healthcare providers, academia, pharmaceutical industry, and public authorities. One participant did not identify with any of the five predefined stakeholder groups in the first Mentimeter question and was therefore named ‘unknown’ when responding to this and subsequent questions raised through this tool.

[209] Austria, Belgium, Cyprus, Croatia, Czech Republic, Finland, France, Germany, Ireland, Italy, Netherlands, Norway, Portugal, Romania, Slovenia, Spain and Sweden.

[210] https://ec.europa.eu/info/sites/default/files/br_toolbox_-_nov_2021_-_chapter_7.pdf.

b. Overview of results from the PC, surveys and interviews

General results

The consultation activities reaffirmed that the main problems affecting the two regulations are closely interconnected. For instance, primarily, the stakeholders highlighted concerns regarding the **insufficient economic interest** from companies and **limited funding for research**. While stakeholders expressed concerns about the **limited capacity of the regulatory framework** within the Paediatric Regulation to foster innovation, they agreed that *both* regulations present significant problems regarding a **lack of science in the definition of UMN**. Some stakeholders (in particular patients and academics) stated issues such as 'economic and operational difficulties', a high rate of waiver and/or deferrals, insufficient rewards and incentives, differences in rules across the EU, as well as limited access and availability of medicines which applied to *both* Regulations.

Paediatric Regulation

i. Paediatric investigation plan (PIP)

During the interview programme, stakeholders (in particular academics and industry) called for smoother and more efficient PIP procedures, better coordination of the committees (particularly highlighted by the pharmaceutical industry) and faster opinion delivery. Regarding the latter point, the stakeholders from the pharmaceutical industry and academia emphasised that while the opinion on a PIP can be delivered in 60 days, in practice, most PIPs are delivered in 120 days.

With regards to the ***deferrals***, results from the interview programme revealed that deferrals were considered needed for ethical reasons, trial recruitment and formulation issues, and for finalisation of toxicological evaluations, as noted by the pharmaceutical industry, public authorities and academia. Some interviewed representatives from public authorities and academia mentioned ways to possibly reduce deferrals. The suggestions included transferable vouchers, tax credits and other factors outside the Paediatric Regulation (improvement of trial preparedness, standardisation of health data and health data records to provide evidence).

ii. Unmet Medical Needs (UMN)

With regard to UMN, the targeted surveys and interviews covered the following subtopics: (1) criteria for UMN, (2) systems to identify UMN, (3) measures to develop medicines for UMN, (4) research and development support to UMN, and (5) novel rewards for products addressing UMN. At the same time, the OPC consulted stakeholders on subtopics (1), (3), and (4). Overall, stakeholders continue to consider UMN a serious issue within the Paediatric Regulation.

With regards to the ***criteria*** to define UMN, **around 80 %** of *all stakeholder groups* participating in the Option Surveys indicated that the **'seriousness of the disease'** and **'no authorised treatment for the disease available'** should be included among the most relevant criteria for defining paediatric UMN, while interviewees and OPC respondents generally considered all criteria[211] important when defining paediatric UMNs. Some interviewees cautioned *'not to define it too narrowly through a legislation'*; other interviewees explained that there is a need for a flexible framework to identify UMN. Importantly, the issue of **appropriate formulation** of products was raised by several interviewees.

[211] Seriousness of the disease (life-threatening and/or seriously debilitating and/or chronically and progressively leading to a seriously debilitating status). No authorised treatment for the disease is available (therefore, a clear need for any treatment for a disease), and no commonly used method that would not be subject to marketing authorisation is widely available (e.g., surgery). Treatments are already available, but the corresponding therapeutic efficacy and/or the safety would need to be significantly ameliorated. Treatments impose an elevated treatment burden for patients. Available treatments are not addressing unmet medical needs in all paediatric ages (e.g., adapted doses and / or formulations / routes of administrations specific to neonates).

With regard to the systems to identify UMN, the general attitudes revolve around UMN being **difficult to define** (particularly among industry and academia) and that this ought to be done in a **multi-stakeholder approach**. Furthermore, the public authorities consulted in the Options Survey provided some suggestions on mechanisms to *better* identify paediatric UMN: **modifying the system of incentives**, **expanding and better monitoring the off-label use of medicines for children**, and **directly engaging with patient representatives and healthcare providers**.

In the Options Survey, the respondents stated that there is a **need to revise a rewards and incentives system**, create **research-driven funds**, and **modify a waiver system**. In addition, a need to introduce a **possibility to link the six-month Supplementary Protection Certificate (SPC) extension** to the timely completion of a PIP and/or the extension by two years of the market exclusivity for paediatric medicines is not an alternative to the six-month SPC extension was noted.

i. Mechanism of Action criteria

During the consultation activities, various stakeholder groups emphasised the need for paediatric drug development to be driven by the mechanism of action (MoA) via a revision of the conditions for granting a waiver. Such a system was supported by academia (91% of correspondents), civil society (86% in favour), public authorities (84 % in favour), and healthcare providers (80 % in favour), but there was little or no support from the pharmaceutical industry[212]. Multi-stakeholder discussions should be arranged in order to introduce further changes and strategies. With regards to the therapeutic area, the majority of interviewees were sceptical of going outside oncology. The main concerns related with the need for an adequate level of understanding in biology, the need for considering diseases with the same genetic cause and the difficulty of obtaining reproducible data. Only some public authorities considered this possible.

ii. Rewards and incentives

Stakeholders consulted via the OPC, targeted surveys, and interviews considered an **insufficient reward and incentives system** as one of the main problems affecting the development of paediatric medicines for UMN. In the Option Survey, respondents from academia and the pharmaceutical industry argued that a **novel complementary reward should be introduced and/or the existing rewards and incentives should be modified** to make them more effective, proportionate, and flexible in addressing the market failure in both paediatric and orphan regulatory areas.

Stakeholders who provided responses to the Option Survey suggested that these complementary actions could include **modifications in the pricing policy**, which, in their view, should aim to assign economic value to any new paediatric indication derived by new clinical research as well as **innovation and investment in off-patent paediatric developments.** Within OPC, stakeholders suggested designing new solutions based on case studies on how antimicrobial resistance (AMR) research and development are incentivised and expeditated, for instance, through pull incentives as well as establishing negative incentives for companies (under revocation of patent protection) if they do not implement these voluntarily. Further complementary actions, such as early rewards or sharing of the resulting data, were also mentioned.

iii. Research priorities

In the Option Survey, nearly half of the respondents from academia (41 %) stated that the **EC should set future research priorities**, whereas slightly more than a third of the respondents (35 %) thought that they should be set by national health agencies and public authorities.

Some interviewees from public authorities observed that the issue with research, in general, is neither funding nor setting the right research priorities, but rather '*a failure of the demand'*, linked to

[212] Only one response from the pharmaceutical industry was recorded.

failures in clinical research and the issue of a small market. Therefore, improvements to clinical trials and pre-commercial procurement could be useful to address the research and development in specific areas.

iv. Access and availability

In the Option Survey, 60 % of the respondents from civil society and healthcare providers stated that accessibility to paediatric medicines had improved somewhat in recent years[213]. Approximately 23 % of respondents, all from the healthcare providers group, also emphasised that the COVID-19 pandemic affected access to paediatric medicines.

During the Option Survey, stakeholder groups also outlined the main ***barriers*** to the accessibility of paediatric medicines: insufficient public/private investment in research and development for paediatric medicines (25 % of respondents) and strategic commercial decisions by companies (25 % of respondents), followed by national pricing and reimbursement policies (21 %), national drug pricing policies (16 %), and EU-level market authorisation procedures (9 %). Some respondents from the healthcare providers group also outlined that the national procedures for marketing new medicines are taking too much time. Other issues emphasised during the OPC and interview programme by civil society and the EU citizens included lack of access to essential medicines due to shortages, lack of child-friendly formulations, and lack of financial access for newer medicines in some EU countries.

v. COVID-19 impact on paediatric medicines

In the Options Survey, nearly half of respondents (44 %) from all stakeholder groups answered that they encountered **problems affecting paediatric research activities due to the impact of COVID-19**. The impact was most evident as implementation of clinical trials has been paused while the research funding has been reduced. Additional restrictions were further imposed, such as patients' access to hospitals and healthcare services, labs, and face-to-face events. Although only 12 % of the respondents in the Option Survey stated that the pandemic was affecting access to paediatric medicines, during interviews, stakeholders from civil society emphasised that the COVID-19 pandemic had exacerbated the shortage of paediatric medicines and increased the risks of under-cured paediatric patients affected by COVID-19 and its complications.

[213] 32 % of respondents from healthcare providers group emphasised that, in recent years, accessibility had not improved at all or had remained the same.

Orphan Regulation

i. Orphan designation criteria

In general, stakeholders from the pharmaceutical industry emphasised that the **current orphan designation criteria are predictable** and **have been effective** in encouraging the development of products for rare diseases. With regards to the ***prevalence threshold***, a clear message from the consultation programme was that lowering the prevalence threshold would not address UMNs better. As interviewees underlined, products for some rarer diseases (with a low prevalence) are available and while there are none for some more widespread diseases.

With regards to the use of the ***incidence criteria*** for rare cancers and short duration diseases to help focus the development of orphan medicines in areas of UMN, some stakeholders supported the implementation of such criteria; others regarded it as *challenging*. In the Options Survey, slightly more respondents agreed than disagreed with this change (28 % and 25 %, respectively). At the same time, during the interview programme, representatives from academia agreed on the incidence criteria for rare paediatric cancers, and some interviewees from civil society suggested the 'combined use' of both prevalence and incidence to define rare diseases.

With regards to the introduction of a ***cumulative prevalence*** criterion for products with more than one orphan designation, the participants in the consultation programme provided varying views. For example, a new criterion of cumulative prevalence was endorsed by a share of academia and public authority representatives, while other stakeholders from the pharmaceutical industry did not support it. According to the pharmaceutical industry representatives, this was mostly because the developments in more orphan indications and prevalence should not be penalised. They also recognised that the fact that an orphan medicinal product is useful for more than one condition (as happens for cancers) is overall a positive aspect, rather than something to be penalised.

A point that stood out during the interviews was that **the prevalence or incidence criteria for cancers**, according to academia, should *still* define a rare population in the Regulation (including for the tissue-agnostic medicines). Furthermore, representatives from academia suggested the **use of ROI as a criterion in addition to prevalence** (or incidence) and *not* alternatively to prevalence. According to the stakeholder, this would avoid overcompensation. At the same time, public authority representatives suggested considering a threshold (without specifying which one) to possibly prolong the market exclusivity period.

ii. Significant benefit

With regards to ***significant benefit***, different stances were expressed by stakeholders**.** In the Options Survey, the majority of stakeholders from *all* groups (48 %) agreed that **the current rules for demonstrating significant benefit should be modified** to ensure that products provide real benefit**.** Public authorities highlighted that significant benefit should be tightened up and evaluated more strictly, for instance, by requiring proof of clinically relevant effect. Moreover, during the interview programme, public authorities recognised that such rules could be improved as sometimes they are difficult, particularly at the time of marketing authorisation when more robust data are needed, especially in areas such as the following: (i) 'Crowded' areas where there are other treatments available, (ii) Oncology where there are first- or second-line treatments, (iii) Combination therapies, (iv) New formulations that are less convenient for patients, (v) When efficacy and safety could not be compared as at the time of marketing authorisation application, data could be limited, and therefore, it is difficult (and unfair) to compare this limited data with the safety data of another product already on the market for many years, (vi) When the demonstration of significant benefit is based on 'major contribution to patient care'. This sometimes means that previous / available medications may 'harm' patients. In this assessment, it is important to hear the opinion of the patients.

iii. Unmet medical needs (UMN)

With regard to UMN, the targeted surveys and interviews covered the following subtopics: (1) criteria for UMN, (2) systems to identify UMN, (3) measures to develop medicines for UMN, (4) research and development support to UMN, and (6) novel rewards for products addressing UMN. At the same time, the OPC consulted stakeholders on subtopics (1), (3), and (4).

With regards to ***criteria*** to define UMN, many stakeholders participating in the consultation activities confirmed that all proposed criteria are essential. In the Options Survey, the most relevant criteria for defining UMN were **the seriousness of the disease**, **no authorised treatment for the disease is available**, and **no commonly used method that would not be subject to marketing authorisation is widely available**. The pharmaceutical industry suggested that **the ROI criteria can be elaborated further**, and there is a need for **clear guidance on indications and scenarios**. Furthermore, during the interviews, the pharmaceutical industry and civil society considered quality of life as an additional criterion to define UMN.

With regards to the ***systems to identify*** UMN, stakeholders participating in the consultation programme, including the pharmaceutical industry, academia and civil society, tended to agree that the definition of UMN in rare diseases should be **dynamic** and supported the idea of introducing a multi-stakeholder dialogue at a very early stage of the development since the definition varies in content and across different stakeholder groups.

In the Option Survey, three ways to identify unmet needs were proposed[214]. All of the stakeholder groups except for the pharmaceutical industry (45 % of respondents in total) identified ***criteria*** **defining UMN in rare diseases should be established in the EU legislation and detailed in scientific guidelines**, which could be updated regularly as the most appropriate. Public authorities participating in the interview programme specified that such criteria would facilitate work or regulators and make its [*work*] more predictable.

With regards to the **creation of *a list* of UMN**, the conclusion was that the majority of stakeholders see it as *unfeasible*. Civil society specified that such a list could be only valuable for research, while public authorities propose that **a list of 'crowded areas'** would be an easier and more effective option.

iv. Rewards and incentives

Similar to the development and regulation of paediatric medicines, **insufficient rewards and incentives** were outlined as one of the key barriers to developing orphan medicines by most stakeholder groups and pharmaceutical industry in particular during the consultation activities of the OPC, targeted surveys and interviews. All stakeholder groups agreed that the **revision of the current reward and incentives system is needed**.

To revise the current system, respondents from civil society emphasised that the **one-size-fits-all incentive framework is not sustainable** for national healthcare systems. Thus, rewards and incentives should be differentiated**.**

v. Research priorities

Similar to the paediatric Options Survey results, nearly half of the respondents (44 %) from academia, the pharmaceutical industry and public authorities thought that the **EC should be responsible for setting the research priorities**. However, around a third of respondents (31 %) stated that others should be responsible for this task. A frequent suggestion was to involve all

[214] A list of UMN in the areas of orphan medicines in the EU legislation and updated regularly; A definition of UMN in rare diseases in the EU legislation; Criteria defining UMN in rare diseases in the EU legislation and detailed in scientific guidelines, and updated regularly.

stakeholder groups in the process. Likewise, the interviewees from the pharmaceutical industry sustained a '*more integrated approach for fostering research and development'*, as well as an '*ecosystem*' that drives the '*basic research'* and '*transnational research'*. In this context, according to the interviewees, this '*ecosystem*' could be complemented with an '*additional incentive such as a transferrable exclusivity extension, but only in the context of a broad ecosystem*.'

vi. Scientific developments

During the interview programme, the stakeholders were asked to suggest elements to define 'innovative products'. Some suggestions were provided, including: high therapeutic value, new target (new knowledge about the disease), the product itself (e.g. combinations of antibodies, construct which has several elements), delivery (a new and different way to deliver the medicine) and cure versus care.

When asked whether **orphan designation should <u>not</u> be granted to subsets of common diseases** to avoid unnecessary multiplications of rare diseases out of common diseases, the majority of the Options Survey respondents (76 %) from academia and public authorities' groups agreed with this approach.

During the interview programme, it became clear that **a novel scientific-based approach should be used** to define an orphan condition. However, both public authority and industry interviewees recognised that innovation should also be considered outside the Orphan Regulation, and this should include how to get scientific advice early in the development, how to support trial designs in a better way, how to get evidence from Real World Data (RWD), the role of the regulation in innovation, better capacity building and coordination of expertise at EMA level. Finally, industry representatives deemed there is no need for additional measures for similarity assessment for ATMPs.

vii. Efficient procedures

Around 65 % of Options Survey respondents from academia, the pharmaceutical industry and public authorities supported **transferring the responsibility for identifying medicines for use against a rare disease from the EC to the EMA[215].** Some stakeholders who opposed this change[216] stated that they were *satisfied* with the current system. Around half of respondents agreed that this change would result in decreased administrative burden and more efficient procedures, and around a quarter of respondents said it would *not* make a difference. During the interview programme, public authorities assumed that such a transfer of responsibility would not be revolutionary for the *outcomes* of assessments, as there are very few examples when the COMP opinion is not taken over by the EC.

One of the key takeaways from the interview programme in regard to this topic was that the streamlining of procedures is *not* a matter of changes to the Orphan Regulation, but rather, it is a matter of the general regulatory system as a whole (i.e. this should be addressed within the Pharmaceutical Strategy).

viii. Access and availability

The Options Survey results revealed that more than half of the respondents from healthcare providers and civil society groups (63 %) regarded **the accessibility at least as somewhat improved** since 2017. Concerning the barriers that limit access and availability of orphan medicines, healthcare providers and civil society named **insufficient research and development** (28 %) and **strategic commercial decisions by companies** (20 %), followed by the **national pricing and reimbursement policies** (16 %), **companies' strategic (launch) decisions** (16 %), **national regulations** (14 %), and **EU-level procedures** (4 %).

[215] With 16 % expressing strong support.
[216] 14 % of the public authority and 22 % of the pharmaceutical respondents.

With regard to potential solutions, the majority of respondents (78 %) and particularly from academia, healthcare providers and public authorities' groups, suggested in the Options Survey encouraging **companies that lose commercial interest in a medicine to offer it for transfer to another company**. However, during the OPC, stakeholders from the pharmaceutical industry emphasised that companies already engage in licensing deals and transfer their products to another company when there is a shared interest on both sides. Respondents to the survey (68 %) also agreed with **fostering competition from generic and biosimilar medicines by ensuring these medicinal products can enter the market a day after the expiry of the exclusivity period**. This was mainly supported by respondents from the academia, healthcare providers and public authorities' groups. However, it should be noted that during the interviews programme, companies (excluding generic companies) did not consider the increase of generic competition as one of the main concerns relating to the development of orphan medicinal products.

The option to introduce **a limit on the validity of an orphan designation to encourage timely medicine development** gained support from a little less than half of the respondents (48 %), mainly from the academia and healthcare providers groups participating in the Option Survey. All stakeholder groups supported the **harmonisation of procedures on the EU-level** regarding orphan medicines development as raised in all the consultation activities.

ix. COVID-19 impact on orphan medicines

Based on the Options Survey responses, most respondents (39 %) stated that they experienced no problems relating to orphan medicines caused specifically by the COVID-19 pandemic. There were some stakeholder groups that did not know / could not answer this question (29 % of respondents from academia and 21 % of respondents from public authorities). This could be due to the fact that the pandemic is ongoing, and the exact impact cannot be quantified just yet. However, a large proportion of healthcare providers (50 %) thought that the pandemic is affecting **access to orphan medicines**, while 18 % of the public authority respondents stated that COVID-19 is affecting **research activities** relating to rare diseases.

In addition to the negative consequences of the pandemic, many stakeholders highlighted '*lessons learned*' and positive takeaways that could be adapted for the future of orphan medicine development. For instance, the interviewees from the pharmaceutical industry noted that **fostering the utilisation of digital tools** and **telemedicine** could be welcome integrations into the day-to-day practice. However, this would necessitate additional resources for public authorities.

c. Overview of results from the focus group

The focus group discussion was structured around the results of the interactive assessment of **six key questions** focusing on the expected impacts of a selection of changes proposed for the current system of regulatory incentives foreseen under the Paediatric and Orphan Regulations.

On the impact on paediatric products, if the 6-month SPC extension was reduced or abolished, respondents were rather divided among those expecting a proportional decrease in the number of all PIPs and paediatrics products (40%) and those who expected no change (36%). The question was linked to the obligation of completing the PIP. The representatives of national public authorities argued that the **current 6-month SPC extension does not take into account cases when the development of a product takes longer**. Despite the frequency of these cases, the obligation remains the same.

Moreover, **the risk of losing the SPC extension seems not to be enough to accelerate the PIP completion (**32 % of the participants agreed, 46% of participants **did not know or thought that this question was not relevant for them** while the smallest but still significant share of participants (22%) disagreed). Difficulties in recruitment and the complexity of PIPs were mentioned as the main obstacles in the completion of PIPs by industry.

Regarding the impact on products addressing unmet need, if the 10 market exclusivity was reduced or abolished, most participants who responded to this question (62%) expected a **proportional decrease in the number of orphan designations and products**. The need to **review and discuss the possibility to revoke certain incentives granted to the manufacturers** under the current legislation if their impact proves inadequate was recognised, while making the distinction between reduction of incentives and their abolishment. Finally, the representatives of public authorities also highlighted that the current Orphan Regulation **enables repurposing of medicines and many of these medicines are not covered by any patents**. Given this, it is particularly important to consider the intersection between paediatric and orphan products.

Nearly half of the participants in the focus group agreed that the risk of receiving a reduced ME incentive would improve the availability of products actor Member States. However, the decisions related to the availability are not fully in the hands of the marketing authorisation holders. In addition, limiting incentives to products addressing areas of unmet needs was not recognised by all as a way to shift the investments of the industry to those areas: on the one hand, over half of the participants who responded to this question (51%) **disagreed** with the assumption that **limiting incentives to products addressing areas of unmet needs would shift the investments of the industry to those areas**. On the other hand, over a third of respondents (37%) agreed that limiting incentives to products addressing areas of unmet needs would shift the investments of the industry to those areas for both paediatric and orphan products.

Finally, participants were asked to identify which of the proposed solutions regarding the support for the development of products in areas of unmet needs they most agreed with. Most respondents (40%) stated that **no new reward or incentive was needed to support the development of products in areas of unmet needs**. In terms of two different types of vouchers proposed, more respondents supported the introduction of transferable regulatory vouchers (36%) over transferable priority review vouchers (24%). It was also noted that the option involving both vouchers might have been selected by some participants if it was presented among the pre-defined options.

Stakeholders generally agreed that the key issue in the current Paediatric and Orphan Regulations is that the existing measures **do currently incentivise the timely evaluation and development of medicines**. Most agreed that the focus should be on creating a **system that can sustain the existing pathways**, **with some additional measures targeting unmet needs**.

Summary of the focus group discussion

All in all, a need for a holistic approach to the revision of the EU legislation on medicines for children and medicines for rare diseases emerged. There is a need to direct more EU and national research funding to the start-up level to simulate the development of new products and their reimbursement, and make sure they reach patients. Most stakeholders agreed that the current system of incentives and rewards should not be abolished or reduced but rather adapted to the evolving priorities and better tailored with additional conditionality. The introduction of transferable regulatory vouchers has received greater support when compared to transferable priority review vouchers. However, the experience concerning these proposed types of vouchers within the regulatory system remains limited; therefore, a lot of questions concerning the risks of overcompensation, exploitation, unpredictability and time constraints have been raised. Thus, in revising the system, stakeholders asked to dedicate a particular attention to mitigating the risk that new incentives could potentially skew competition or result in other unintended consequences. Finally, given the close links between the revision of the Paediatric and Orphan Regulations and the revision of the General Pharmaceutical legislation, which is being carried out in parallel, all stakeholder groups agreed with the need for further consultations in the upcoming year.

ANNEX 3: WHO IS AFFECTED AND HOW?

1. Practical implications of the initiative

For the Orphan Regulation

The planned revision of the legislative framework on medicines for rare diseases is expected to have an impact on patients, payers/health systems and pharmaceutical companies.

Concerning **patients**, benefits derive from more orphan medicinal products accessible in particular in areas of HUMN.

Originators will benefit from simplified procedures with the Agency and more gross profit from the sales of (HUMN) orphan medicinal products developed. Costs mainly relate to gross profit loss due to the access conditionality and faster entry of generics/biosimilars after the expiry of the market exclusivity. In particular, SMEs will benefit considerably from the simplified procedures.

The legislation will result both in costs for payers/**health systems** (due to the extra year of market exclusivity for HUMN) and in benefits (mainly cost savings of the 1-year of market exclusivity conditionality for non-complying medicines; faster entry of generics/biosimilars).

For the Paediatric Regulation

The planned revision of the legislative framework on medicines for children is expected to have an impact on pharmaceutical industry, health systems/public authorities and patients.

Concerning **patients**, benefits derive from the study in children and of new medicines in particular in areas of UMN resulting (thanks for example to the introduction of the mechanism of action provision) in the avoidance of ADRs and increased quality of life thanks to medicines studied and authorised for children. As explained in section 6 very serious ADR due to the off label use of a product are very rare event and cannot be captured with historical data. While the average impact of ADR could relatively mild, a single very rare case of serious ADR would have the potential to create a thalidomide-like scenario. In addition, specifically researched medicines for use in children may result in breakthrough treatments for diseases for which no treatment at all was available, thereby increasing considerably the quality of life of the affected children, beyond the avoidance of ADRs. As it is not possible to anticipate which products will be developed is not possible to provide a quantitative assessment of this effect. Patient are also expected to benefit a faster access to medicines thanks to a faster completion of the PIPs due to the simplification of the PIP procedure and to the cap of the length of the deferrals.

Pharmaceutical industry are expected to develop more products in areas of UMN for children and at the same time benefit from simplified procedures for agreeing with the Agency on the paediatric development plans which they will have to conduct leading to a reduction of their administrative costs per product developed. .

The legislation will mainly results in direct costs for **public authorities** will mainly due to the costs resulting from the rewards that will be allocated to the products developed thanks to the legislation. However, it should be considered that more products for children are expected to consist in savings from avoided hospitalisation and avoided outpatient treatments. Such benefits were calculated in the Joint Evaluation on the basis of products developed and resulted in minor, almost irrelevant impacts and therefore have not been quantified in this SWD, however, as explained above, the use of non-properly tested product in children may result in catastrophic consequences and in a thalidomide like scenario.

2. Summary of costs and benefits

For the Orphan Regulation

I. Overview of yearly Benefits (compared to baseline benefits – million €) – Preferred Option

Description	*Amount*	*Comments*
Direct benefits		
Pharmaceutical companies (originators)	+€94m gross profit due to +1 year of ME for HUMN medicines	
Pharmaceutical companies (generic industry)	+€38m gross profit gain due to non-complying medicines on launch conditionality +€50m gross profit due to predictable market entry ('day-1') +€13m gross profit due to abolishing 2-year ME for completing PIP	
Public payer/health systems and patients	+€288m cost saving from non-complying medicines access conditionality and broader and faster access to complying medicines +€360m cost saving due to predictable market entry ('day-1') +€96m cost saving legal clarity abolishing 2-year ME for completing PIP	
Indirect benefits		
Administrative cost savings related to the 'one in, one out' approach*		
Direct administrative costs savings	**4.5 m** €	Direct cost saving

*Estimates are gross values relative to the baseline for the preferred option as a whole (i.e. the impact of individual actions/obligations of the preferred option are aggregated together); (2) Please indicate which stakeholder group is the main recipient of the benefit in the comment section;(3) For reductions in regulatory costs, please describe details as to how the saving arises (e.g. reductions in adjustment costs, administrative costs, regulatory charges, enforcement costs, etc.;); (4) Cost savings related to the 'one in, one out' approach are detailed in Tool #58 and #59 of the 'better regulation' toolbox. * if relevant*

II. Overview of costs – Preferred option							
		Citizens/Consumers		**Businesses**		**Administrations**	
		One-off	**Recurrent**	**One-off**	**Recurrent**	**One-off**	**Recurrent**
Costs for +1 year of ME for HUMN products	Direct costs				13 m € loss in gross profits (generic industry)		82 m € additional costs

Costs for 1 year of ME condition for full EU launch	Direct costs				282 m € loss in gross profits (originators) 4 m € additional costs		
Costs Day-1 entry of generic/biosimilars after ME expiry	Direct costs				354 m € loss in gross profits (originators)		
Costs Abolishing 2-year ME extension for completing PIP	Direct costs				94 m € loss in gross profits (originators)		
Administrative costs due to increased number of orphan designations					1.3 m €		
Costs related to the 'one in, one out' approach							
Total	Direct adjustment costs	N.A	N.A	N.A	N.A		
	Indirect adjustment costs	N.A	N.A	N.A	N.A		
	Administrative costs (for offsetting)	N.A	N.A	N.A	**1.3 m** €		

(1) Estimates (gross values) to be provided with respect to the baseline; (2) costs are provided for each identifiable action/obligation of the preferred option otherwise for all retained options when no preferred option is specified; (3) If relevant and available, please present information on costs according to the standard typology of costs (adjustment costs, administrative costs, regulatory charges, enforcement costs, indirect costs;). (4) Administrative costs for offsetting as explained in Tool #58 and #59 of the 'better regulation' toolbox. The total adjustment costs should equal the sum of the adjustment costs presented in the upper part of the table (whenever they are quantifiable and/or can be monetised). Measures taken with a view to compensate adjustment costs to the greatest extent possible are presented in the section of the impact assessment report presenting the preferred option.

For the Paediatric Regulation

The figures cited in the tables below illustrate the benefits and the costs under the preferred options in relation for the affected stakeholders. They are based on the assessment of costs and benefits described in Section 6.2 and Annex 4 section 7.

The figures are presented in comparison with the baseline and are average annual costs in m€

I. Overview of benefits (compared with baseline costs) – Preferred Option. Yearly costs		
Description	***Amount***	***Comments***
Direct benefits		
Industry, originators	169 m gross benefit	Benefits deriving from one estimated SPC extension per year
Patients	3 extra PIPs for products addressing UMN of children Faster completion of PIPs and consequently medicines reaching faster children	Not possible to determine the benefits as it will depend greatly from the products that will be developed
Administrative cost savings related to the 'one in, one out' approach*		
Direct Administrative costs savings	**2.8 m**	Administrative savings for companies deriving from the simplification and streamlining of the PIP procedures

II. Overview of costs (compared with baseline costs) – Preferred option							
		Citizens/Consumers		**Businesses**		**Administrations**	
		One-off	**Recurrent**	**One-off**	**Recurrent**	**One-off**	**Recurrent**
Costs for conducting extra PIPs for originators	Direct costs				66 m €		
Cost for delayed generic entry due to one extra SPC paediatric extension granted per year					33 m €		
Costs for public authorities due to the extra SPC paediatric extension granted					1.3 m €		76 m €
Costs for patients			75 m €				

due to the extra SPC paediatric extension granted leading to delayed entry							
Administrative costs due to increased number of PIP conducted					1.3 m €		
Costs related to the 'one in, one out' approach							
Total	Direct adjustment costs	N.A	N.A	N.A	N.A		
	Indirect adjustment costs	N.A	N.A	N.A	N.A		
	Administrative costs (for offsetting)	N.A	N.A	N.A	1.3 m €		

3. Relevant sustainable development goals

III. Overview of relevant Sustainable Development Goals – Preferred Option(s)		
Relevant SDG	**Expected progress towards the Goal**	**Comments**
SDG no. 3 – Good health and wellbeing	Support the research and development of vaccines and medicines for the communicable and non-communicable diseases that primarily affect developing countries, provide access to affordable essential medicines and vaccines, in accordance with the Doha Declaration on the TRIPS Agreement and Public Health, which affirms the right of developing countries to use to the full the provisions in the Agreement on Trade Related Aspects of Intellectual Property Rights regarding flexibilities to protect public health, and, in particular, provide access to medicines for all	
	Strengthen the capacity of all countries, in particular developing countries, for early warning, risk reduction and management of national and global health risks.	
	Achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential	Increase of medicines especially in areas of HUMN and paediatric medicines

	medicines and vaccines for all.	
	By 2030, reduce by one third premature mortality from non- communicable diseases through prevention and treatment and promote mental health and well-being.	
	By 2030, end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases.	
SDG no. 9 – industry, innovation and infrastructure	Enhance scientific research, upgrade the technological capabilities of industrial sectors in all countries, in particular developing countries, including, by 2030, encouraging innovation and substantially increasing the number of research and development workers per 1 million people and public and private research and development spending.	

ANNEX 4: ANALYTICAL METHODS

Given the harmonised revision of the orphan and paediatric regulations together with the general pharmaceutical legislation along the same objectives, the methodology and models largely build on the impact assessment of the *general* pharmaceutical legislation[217].

1. Data sources

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

Literature and document review: we have carried out a targeted literature and document review of academic and grey literature, using specific topics of each policy option, such as access to medicines, to guide our searches. There is a growing body of published literature and analysis reports that studied specific phenomena relevant to aspects of the pharmaceutical legislation. These provide a direct source of facts and figures that we used in our assessments and referenced across the report. Wider literature relevant to newer challenges for the pharmaceutical industry were also reviewed in order to identify future proofing challenges, resilience of supply chains, new manufacturing methods, combination products, digitalisation, new evidence requirements by regulatory authorities and environmental protection.

Secondary data analysis: quantitative data collected along the medicinal product lifecycle was analysed to derive a set of indicators and feed quantitative modelling of various policy scenarios. For problem analysis and baseline, we used data, where available, for the period of 2005-2020 from the IQVIA MIDAS dataset, Informa Datamonitor and Pharmaprojects, EMA's central Marketing Authorisation Application dataset, MRI decentralized / mutual recognition procedures database and EudraGMP.

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

2. Identifying and selecting significant impact types

We carried out an initial screening of the 35 impact types set out in the Better Regulation toolbox to identify the impacts the study will be reviewing more in depth for each policy block with each policy option. We used findings from the various analytical strands and data sources to identify all potentially important impacts, considering both positive/negative, direct/indirect, intended/unintended as well as short-/long-term effects. Specifically, our screening was based on the principle of proportionate analysis and considered the following factors.

- The relevance of the impact within the intervention logic
- The absolute magnitude of the expected impacts
- The relative size of the impacts for specific stakeholders
- The importance of the impacts for the EC's horizontal objectives and policies

[217] Staff Working Document – Impact assessment on the general pharmaceutical legislation (Annex 4).

- Any sensitivities or diverging views

This screening identified 8 of the 35 impact types as being of most significance for this impact assessment and therefore a deeper assessment was appropriate for the following key impact types:

- Conduct of business
- Administrative costs on businesses
- Position of SMEs
- Sectoral competitiveness and trade
- Functioning of the internal market and competition
- Innovation and research
- Public authorities
- Public health & safety and health systems

3. Modelling changes in market exclusivity vis-à-vis regulatory data and market protection system

a. Protection types and length in a sample of medicines

A basket of 217 products was selected based on IQVIA Ark Patent Intelligence data where the loss of protection (LOP) date was between 2016-2024 in four countries: France, Germany, Italy, and Spain. We chose this sample because in earlier years the regulatory protection system was not fully harmonised due to the legacy of the pre-2005 system. This sample has an additional benefit of having a prospective feature, in that it shows, based on empirical data, the composition of the most recent and also the expected future protection expiries of medicinal products.

In the basket, there have been 26 orphan medicines, and Figure 1 demonstrates how the protection types and lengths vary among them. These tables omit regulatory data and market protection (RP) because in the case of an orphan medicine the 10-year RP protection is matched by the 10-year market exclusivity protection (ME). Despite the same nominal lengths, the ME allows a couple of months longer protection, because it does not allow (yet) generic medicines to apply for authorisation before ME expiry. RP permits generics to start the authorisation earlier, so they can enter the market right after protection expiry.

Figure 10 – Length of protection of orphan medicines by type of protection

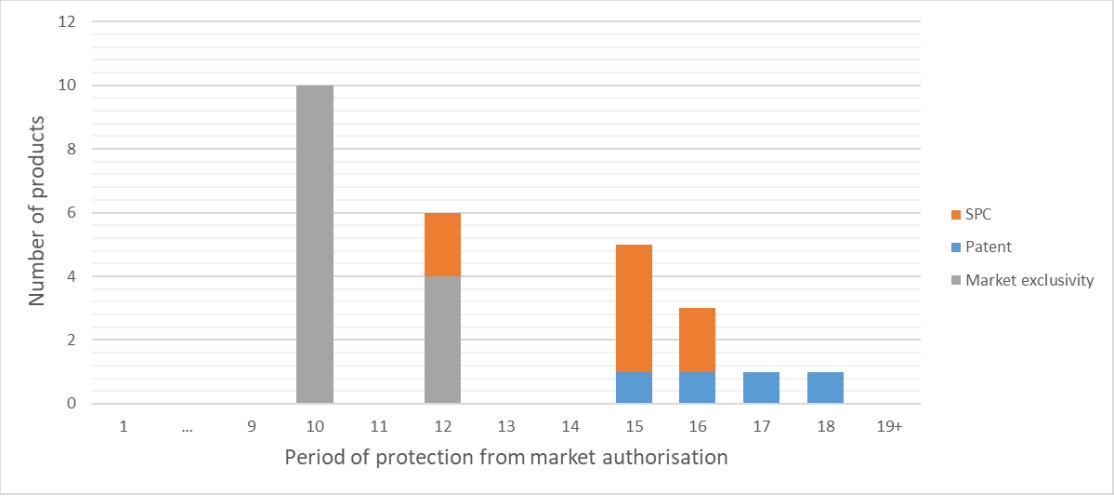


Table 24 - Length and type of protection of orphan medicines

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

Similar to the findings of the general pharmaceutical impact assessment, Table 1 demonstrates that SPC and patent protected medicines have a longer protection type, and usually generate higher revenues, whereas products with ME are characterised by shorter protection (10 or 12 years if paediatric studies have been carried out) and lower revenues. In our sample, market exclusivity protected products (14 out of 26) make up more than 50% of all products, but only 11% of the total sales.

Consequently, changes to the market exclusivity (unless making it longer than SPC protections) would not affect SPC and patent protected medicines, thus limiting the economic impacts at systemic level. Nevertheless, changes may have significant impact on certain affected companies.

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

In the general pharma impact assessment a key foundation of the model is a carefully crafted analogue. The analogue takes longitudinal sales data from a basket of medicines that meet certain criteria. For the general pharma this basket was made of RP protected medicines, however orphan medicines with 10-year protection were also eligible for inclusion. The analogue was generated from the weighted and normalised average sales values (in euros) and volumes (in standard therapeutic units) of the medicines in the cohort. To put it simply, the analogue behaves as a typical representative of that basket.

The analogue captures the lifecycle of innovative products over the protected period and that contested by generic/biosimilar medicines after protection expiry. Since ME protected medicines are similar to RP protected medicines in that they also have 10-year protection, and because they have been already included in the general pharma analogue, we have decided to use the same analogue with a slight adaptation. This adaptation is necessary due to the lower revenue generating capacity of non-SPC protected orphan medicines, a different avg. peak annual sales value is needed than in the RP model. After filtering out some very low sales (less than 10M) orphan medicines from the cohort, we have found an avg. peak annual sales of €80 m for ME protected medicines.

In order for sales revenues (euros) and volumes (standard units) across the pre-expiry and post-expiry cohorts and periods can be joined up and compared, aggregate absolute values were normalised so that the originator products' total sales and volume become equal to 100 at one year before protection expiry (Y-1).

A particular challenge is that sales revenues do not give the full picture of company benefits. The driver of businesses economic activity is not the revenue but the profit. Gross profit appears the most adequate and comparable measure, it is the cost of sales deducted from the revenues. The gross

profit only includes the variable costs of manufacturing and distribution, but not the fixed costs, such as R&D and investment in infrastructure. In our model we distinguish three categories of revenues, each with a different margin of gross profits.

- **Protected originator sales**: this is the most profitable category during the protected period of new medicines. Based on a sample of reports from publicly listed companies we apply a 80% gross profit margin on the revenues (20% cost of sales)

- **Contested originator sales**: once generics enter the market, originator products are forced into price competition. Still, originator products can maintain a price premium compared to generics albeit reduced thanks to brand loyalty and strong sales force. We assume a 50% gross profit margin in this category.

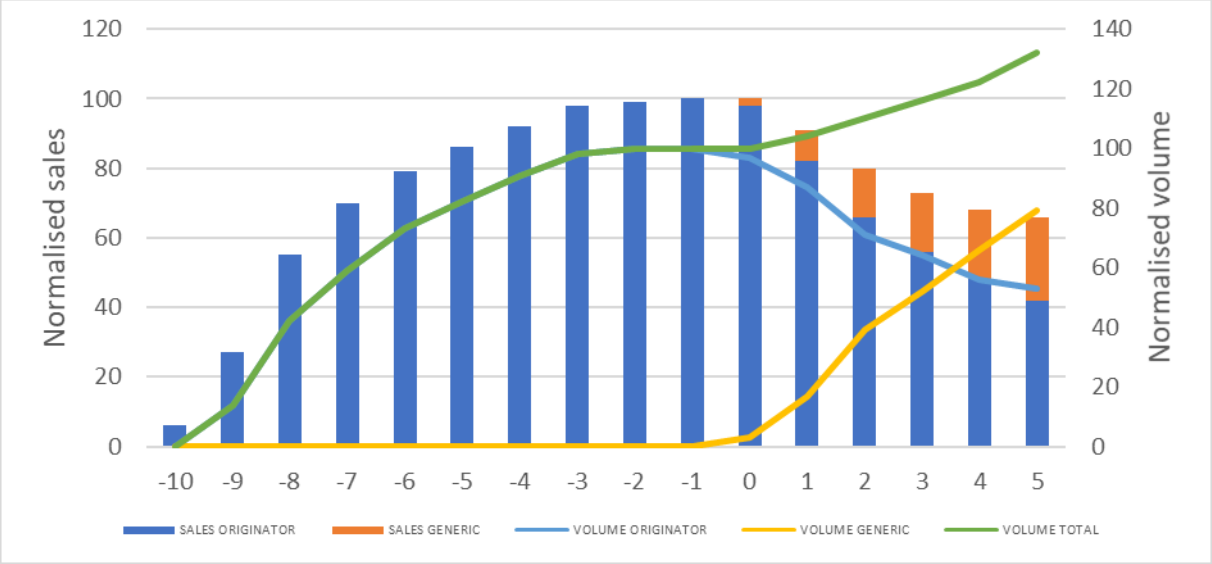
- **Generic sales**: generic industry operates on a high volume, low margin basis. With low product development risk, a lower profit margin can be sustainable. We apply a 33% gross profit margin on generic revenues.

The resulting table and corresponding figure are shown below:

Table 25 - Normalised sales, volume, gross profit and price for products with ME as last measure of protection

Year from expiry	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0	1	2	3	4	5
Originator sales	6	27	55	70	79	86	92	98	99	100	98	82	66	56	48	42
Generic sales											2	9	14	17	20	24
Total sales	**6**	**27**	**55**	**70**	**79**	**86**	**92**	**98**	**99**	**100**	**100**	**91**	**80**	**73**	**68**	**66**
Originator volume	0	14	42	59	73	82	91	98	100	100	97	87	71	64	56	53
Generic volume											3	17	39	52	66	79
Total volume	**0**	**14**	**42**	**59**	**73**	**82**	**91**	**98**	**100**	**100**	**100**	**104**	**110**	**116**	**122**	**132**
Originator profit	4.8	21.6	44	56	63.2	68.8	73.6	78.4	79.2	80	49	41	33	28	24	21
Generic profit											0.66	2.97	4.62	5.61	6.6	7.92
Originator price		1.93	1.31	1.19	1.08	1.05	1.01	1.00	0.99	1.00	1.00	0.94	0.93	0.88	0.86	0.79
Generic price											0.67	0.53	0.36	0.33	0.30	0.30
Average price		1.93	1.31	1.19	1.08	1.05	1.01	1.00	0.99	1.00	1.00	0.88	0.73	0.63	0.56	0.50

Figure 11 - Normalised sales and volume for products with 8+2 years of RP protection (baseline)



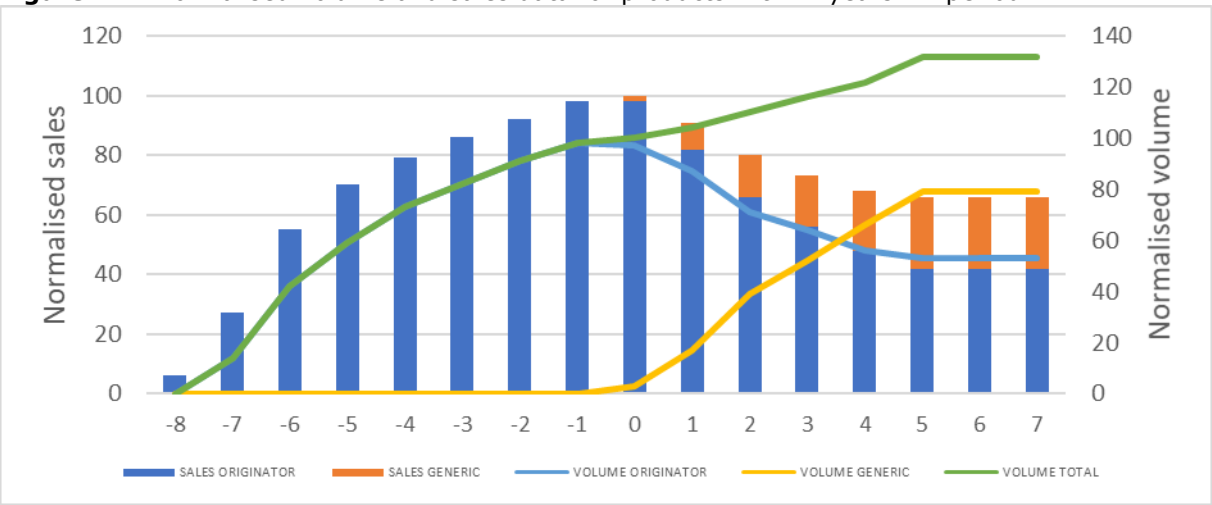
It is evident from the graph that sales revenue and volume grow year-on-year over the 10-year RP period as (i) the product is taken up by the health system and make it accessible to increasingly more patients; and (ii) product is launched in increasingly more member states. It should be noted that health systems may require a number of years before the product becomes accepted by health professionals and routinely prescribed. However, these effects are expected to reach a plateau within a couple of years of introducing the product in a market, and indeed the figure shows that by Y-3 sales figures are close to peaking. The last year before expiry therefore accounts for 14% of total protected sales; while the final two years account for 28% of total protected sales.

c. Modelling the economic impact of decreasing regulatory protection

Some options and common elements include a reduction of the length of market exclusivity. Because even in the revised general pharma regulation the RP would ensure a minimum 8-year protection for all medicines, the maximum lost protection due to shortened market exclusivity is 2 years. This will be the new scenario for the analogue. In the model, we assume that after 5 full years of generic competition an equilibrium value of annual sales and volume of product sold are established and thus we can use Y5 data for originator and generic products as long-term level to calculate the value of ME loss over the product lifetime.

We also assume that the pre-expiry sales trajectory is not changed by company behaviour and thus the baseline Y-1 and Y-2 sales are lost under the new standard ME regime. In the figure below thus the original Y-1 and Y-2 values are removed and Y6 and Y7 values are added at equilibrium level. In addition, we assume that the market dynamics of generic competition (between Y0 and Y5) in the new standard ME regime will not change compared with the ME period of 10 years.

Figure 12 - Normalised volume and sales data for products with -2 years ME period



	Baseline	-2 years ME	change	change %
Originator protected sales	712	513	-199	-28%
Originator contested sales	392	476	84	21%
Originator profit	765.6	648.4	-117	-15%
Generic sales	86	134	48	56%
Generic profit	28.38	44.22	16	56%
Cost to public payer	1190	1123	-67	-6%
Volume (patients served)	1343	1407	64	5%
Cost of additional patients	0	44	44	
Cost of baseline volume	1190	1079	-111	-9%

Using the above model for the product lifetime, we can make the following observations at product level:

- Originator companies' pre-expiry sales loss of -199 (normalised units) over two years is partially compensated by the post-expiry gain of +84 (calculated at the equilibrium level) over two years, giving a net loss of -115 (normalised units) over the lifetime. In other words, originators lose 28 % of their protected sales when the protection is shortened by 2 years. This translates to a decrease in originator's gross profit of -117 (normalised units), which is a 15% loss over the product lifetime, approximated as a 16-year period.

  We know that pharmaceutical industry is one of the most R&D intensive sector and they reinvest a large share of their revenue into innovation for new products and technologies. This share is 20% on average globally[218] and we can assume that the revenue loss will translate to a loss of innovation budget and thus a loss of development of new innovative products and/or incremental (i.e. cheaper) product innovation (e.g. for combination products or new formulations).

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

- Generic companies' start to benefit from sales two years earlier compared to baseline, and thus reach equilibrium level two years earlier. These two extra years of equilibrium generic sales of +48 (normalised units) are equal to +16 (normalised units) gross profit gains.
- Healthcare payers pay less overall due to a decrease in the average price they need to pay for a standard unit of the product. In the baseline 10-year ME regime, the total lifetime sales is 1190 (normalised units) and in the new 8-year protection regime the same volume at the new prices would be 1079 (normalised units). Thus in the new situation healthcare payers would pay -111 (normalised units) less, which is -9% less when considering the lifetime sales of the product.

  In the real situation, however, healthcare payers may not realise this nominal saving but choose to purchase more units of the medicine at a lower price for the healthcare system and expand coverage of patients. This can be considered that payers 'reinvest' part of the savings in the same market and increase purchase of generic products at higher volumes for the benefit of the patient. We can thus calculate the total real sales of originator plus generics product volumes, which can be used to monetise patient benefit. Under the baseline situation, total sales value over the product lifetime is 1190 (normalised units), while under the 8-year protection regime it is 1123 (normalised units), equating to -67 (normalised units) or -6% saving to healthcare payers, on the products that are ME protected. Note, however, when considering the ME protected medicines represent less than 5% of the pharmaceutical expenditure, and that from the total healthcare systems spending in the EU, the pharmaceutical expenditure represents less than 20% (see Analytical report Figure AFF-3, OECD Health Statistics), the savings at the healthcare system level would be marginal.

- Patients benefit due to the increased volume of the medicine sold after ME expiry (2 years earlier) which then reach more patients creating higher level of health benefits. In the model, the total volume increases as soon as generic products enter the market and volume of generic products surpasses that of the originator product by year 4 after generic entry. In the new regime the total volume sold increases by +64 (normalised units) or 5% over the product lifetime above the baseline of 1343 (normalised units) under the 10-year ME regime. However, the extra volume of products available to patients manifest itself in the transition period between expiry and reaching the equilibrium value.

i. Monetising the systemic effects for protection loss due to abolishing ME (Option B)

Option B would result in a 1-year protection loss for orphan medicines that are launched in all EU countries and a 2-year loss for those that are not, because of the revised regulatory protection in general pharma. In accordance with baseline projections, we expect 10 orphan medicines annually where the market exclusivity is the last layer of protection of these, we expect that 4 would comply with market launch in all Member States and 6 would not. Table 7 shows the economic impacts per stakeholder.

Table 26 – Economic impact of no market exclusivity in combination with changes of regulatory protection

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

Patients + payer monetised gain/loss	**+€48m**	**+€89m**	**+€725m**

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

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

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

ii. Monetising the systemic effects for protection loss due to not launching in all EU markets (Option C)

Option C offers the same market exclusivity period for standard orphan medicines as the baseline, 10 years, but only if the medicine is launched in all EU markets within 2 years of authorisation. If not launched in all markets, the protection period is 9 years. This aims to motivate companies to launch in all EU member states, and not to leave out small markets, which are not attractive enough commercially. Similarly to the general pharma revision, it is expected that some medicines will not comply with the access incentive conditions. Given the lower level of baseline compliance of orphan medicines reliant on ME compared to non-orphan medicines reliant on RP, the gap to be bridged will be larger. The assumption is therefore made that 40% of orphan medicines will comply (for non-orphans it is 50%[219]), and 60% will not. Thus, of the 10 orphan medicines expected to have ME as last line of protection, we expect that 4 would comply with market launch in all Member States (and 6 not).

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

No distinction is made here between HUMN and non-HUMN ME-reliant orphan medicines (the total of 10 includes both), since in either case, the length of protection will be increased by one year if the access conditionality is met as compared with those that do not comply. The table below therefore accounts for both cases. Using our model, the impact of 1-year less protection in case of non-launch in all Member States is the following:

Table 27 – Impact of change of -1 year market exclusivity in case of non-launch in all MS

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

[219] General pharma IA SWD, Section 8.1.

For the public payer/patient this instrument is a win-win, if medicines comply, timely access across the EU will increase, and if not, the protection period decreases, lowering cost for society by 48m. The decreased protection translates to 47m lower gross profit per medicine, or 282m for the whole innovative industry.

iii. Monetising the systemic effects for protection loss due to allowing day-1 generic entry (common element)

Allowing entry of generic medicines as soon as market exclusivity is expired, means that an **application for authorisation** of a generic version of the medicine **can be submitted** during the protection period, and can enter the market right after expiry of the market exclusivity. Currently, generic versions of orphan medicines cannot start the authorisation process before the market exclusivity expires[220]. This creates a windfall protection of at least 9 months beyond the 10 years ME, equal to the time needed to authorise a generic medicine from submission[221]. It is estimated that 10 out of the expected 25 new orphan medicines would be impacted per year, the ones where ME is the last layer of protection. Apart from legal certainty for generics it would mean up to €360m savings to the public. Originators would lose their windfall profits by €354m. See Table 11 for the financial impacts of day-1 entry of generic medicines on all stakeholders.

Table 28 – financial impacts of day-1 entry of generic medicines	**Systemic change (10 medicines)**
Originator gross profit	**-€354m**
Generic gross profit	+€50m
Cost to public payer	**-€200m**
Δ of patients treated (monetised)	+€160m
Patients + payer monetised gain/loss	**+€360m**

iv. Monetising the systemic effects for protection loss due to abolishing paediatric ME extension (common element)

Abolishing the orphan market exclusivity extension[222] for completing PIPs will better regulate a system that is currently not functioning very well. At present, the paediatric regulation offers 6 months of SPC extension for completing a PIP, and for orphan medicines 2 years of market exclusivity extension. However, there are several SPC protected orphan medicines with 13-14-15 years of protection duration[223]. Obviously, for these products a 10+2 years market exclusivity is of less value and they would be better off with a 6 months extension of the SPC protection. To switch to this protection, they need to renounce their orphan designation and they often do so. The abolition of the paediatric extension of market exclusivity is thus expected to improve clarity in the system.

Table 29 – Impact of abolishing 2 years ME extension for completed PIP	**Systemic change (1 medicine)**
Originator gross profit	**-€94m**
Generic gross profit	+€13m

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

Cost to public payer	**-€54m**
Δ of patients treated (monetised)	**+€42m**
Patients + payer monetised gain/loss	**+€96m**

The measure will also imply that orphan medicines not protected by SPC but eligible to complete a PIP, will lose the 2-year extra market exclusivity protection available in the baseline. However, from the entry into force of the Paediatric Regulation up to 2020, only 11 of these market exclusivity extensions were granted[224], meaning that it has been a rarely used incentive. With 1 such incentive not granted per year in the future, the public would save €96m per year. The affected originator companies would lose €94m in gross profits over the medicine's lifetime each, but due to the few uses, the impact on the whole industry is not significant.

Caveats to the model used:

Data: IQVIA MIDAS data includes sales revenue data corresponding to list or ex-manufacturer price without accounting for rebates or discounts (especially in hospital sector) on the one hand and costs including wholesale, distribution, value-added tax and social security expenses on the other to healthcare payers.

Opportunity cost: We present data at current euro level without inflation or cost of capital / commercial risk accounted for. This latter is a factor for commercial actors where monetary gains and losses are normally discounted in business calculations and may change decisions related to product developments accordingly. In contrast, healthcare payers pay on an ongoing basis.

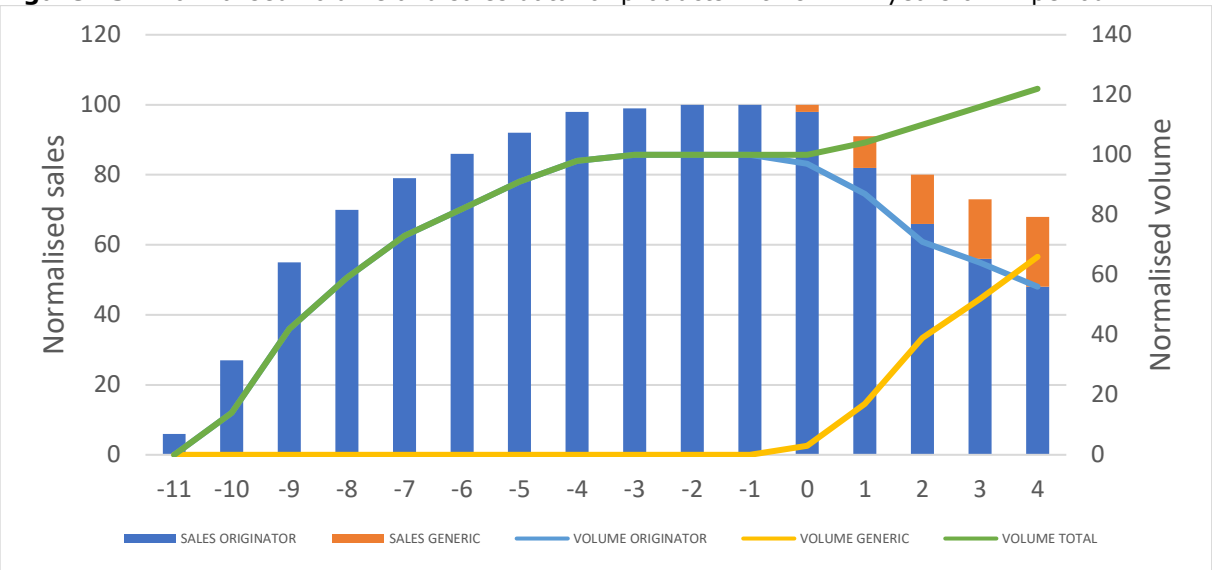
Business behaviour: There may be changes in the trajectory pre- or post-expiry compared to the current RP 8+2 regime, because companies change behaviour and aim to earn similar level of total pre-expiry monopoly rent during the reduced RP period. This may be achieved by entering more markets earlier leading to the same pre-expiry overall sales and volumes of product sold. There is however the risk that the shorter RP period will lead to higher negotiated prices and relatively lower volumes of product sold in the pre-expiry period, or even a reduction in the number of products that enter EU markets.

d. Modelling the economic impact of increasing market exclusivity protection

We use the same data as presented above and assume that after the Y-1 there will be an additional year of peak sales protected by a 1-year ME period. We will use the result of this model to estimate the proportionate effect of the 1 year incentive for HUMN addressing medicines. We assume that pre-expiry sales trajectory is unchanged, the market dynamics of generic competition post expiry is unchanged. In the figure below thus data associated with a new Y-1 is added and the baseline Y5 is removed to maintain the overall product lifetime of 16 years.

[224] EMA data.

Figure 13 - Normalised volume and sales data for products with 8+2+1 years of RP period



	Baseline	+1 year ME	change	change %
Originator non-contested sales	712	812	**100**	14.0%
Originator contested sales	392	350	**-42**	-10.7%
Originator gross profit	765.6	824.6	**59**	7.7%
Generic sales	86	62	**-24**	-28%
Generic gross profit	28.38	20.46	**-7.9**	-28%
Cost to public payer	1190	1224	**34**	2.9%
Volume (treated patients)	1343	1311	**-32**	-2.4%
Patients + payer monetised gain/loss	1190	1241	**51**	4.3%

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

Using the above model for the product lifetime, we can make the following observations at product level:

- Originator companies increase pre-expiry sales due to additional year of monopoly sales by 100 (normalised units) or 14% of lifetime protected sales. In terms of gross profit, this is 47 more monetised unit, or a 7.7% increase.
- Generic companies' start to benefit from sales one year later, and thus generic sales are reduced by 24 (normalised units), and gross profit is reduced by 8 (normalised unit) which is equal to a reduction of 28% sales, compared to baseline.
- Healthcare payers pay more overall due to an increase in the average price they need to pay for a standard unit of the product. We consider again the 'peak' volume sold of the originator product pre-expiry in baseline and use the average price in each year under the different RP regimes to calculate sales. The total cost for healthcare payers is thus -51 (normalised units) over the product lifetime compared to baseline
- Patients lose -32 (normalised units) in decreased volumes of the medicine over the lifetime of the product compared to baseline

i. Monetising the systemic effects for 1-year ME extension for medicines addressing HUMN (Option C)

In accordance with baseline projections, we expect that from the 10 orphan medicines annually where the market exclusivity is the last layer of protection, this measure would affect 20% or two products, which would address HUMN and therefore be eligible for the extra year.

Table 30 – Impact of change of +1 year market exclusivity protection

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

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

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

The cost of a +1 year protection for HUMN protection would be shared among generic industry, health payers and patients. With 2 of such incentives annually, the generic industry would lose €38m in revenues a year, which translates into €13m decrease in gross profits. The health payers would need to pay €54m more on an annual basis. The model also accounts for the patients that would not be served due to the higher prices that result from extended protection. Accounting for that effect too, the cost for the public would rise by €82m annually.

Apart from the monetary impacts stemming from the increased market exclusivity period, we also estimated the number of additional medicines coming to the market. The incentive has two effect: (1) it generates more resources for innovators, (2) it makes the EU market more attractive to medicines that otherwise would not come to the market (there are several orphan medicines annually that are only launched in the US market and not in the EU). As a result of subtle and complex effect pathways, we could not identify directly available literature evidence or model. F

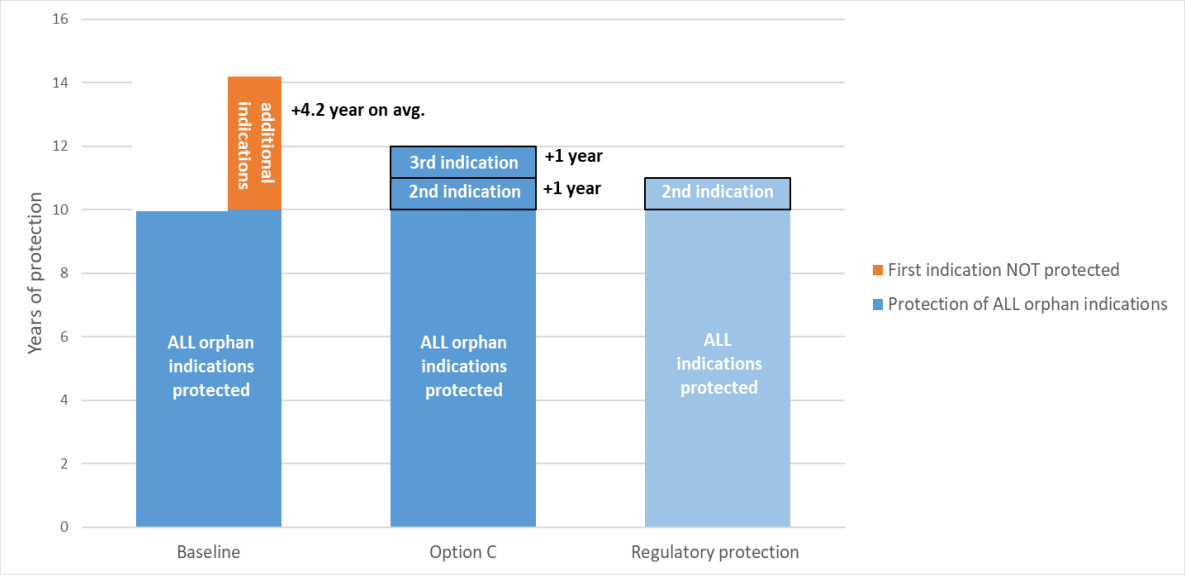
4. Global marketing authorisation

The introduction of the global marketing exclusivity (GMA) will limit stacking market exclusivity periods for additional orphan indications. GMA prolongs the existing market exclusivity by only 1 year in all orphan indications. The use of this incentive is maximised at two indications, i.e. maximum 2 years of prolongation of the ME will be possible. Furthermore, market exclusivity granted **to a second generation product** that is similar to the first generation product will not be applied in respect of generic products of the first reference product for which the market exclusivity expired to avoid so called evergreening[225].

[225] See also Section 5.2 of this SWD.

The GMA would concern 16% of orphan medicines, those with multiple orphan indications. For them it would mean replacing 4.2 years of partial protection for additional indication with on average by 1.3[226] years complete protection of the medicine. Importantly, this would put a limit on 'orphan blockbusters' with several indications, and disincentives on gaming the system for artificially inflated protection periods.

Figure 14 – protected indications under GMA and RP



5. Regulatory data protection vouchers

Overview

Option A envisages a transferrable regulatory voucher as an incentive for originators of products that address high unmet need (HUMN) in rare diseases and diseases in children. The voucher would grant a one-year RDP extension for one medicine. The company awarded the voucher would be allowed to sell on the voucher to another company. For the voucher to be of value, the purchaser must hold a medicine that is reliant on RDP as last line of protection. For products where the SPC or patent expires a year or more after RDP, such a voucher would be of no value.

This section sets out the methodology used to calculate the impact of a voucher scheme for various stakeholders. The analysis highlights the key shortcoming of this form of incentive, namely that the rent generated by the voucher will be shared between the voucher seller and the voucher buyer. Moreover, as the number of vouchers issued increases, the share of the seller declines very quickly. However, the reward to the seller is the intention of the scheme. The reward to the buyer is a by-product. Vouchers come at a significant cost to public authorities, who have to a protection premium on the medicines that use them for an additional year. The more of that additional expenditure that goes to the buyer rather than the seller, the less efficient the scheme.

[226] The weighted average of protection for medicines with one or more additional indication

The methodology set out below aims to simulate the economics of a market for vouchers on the basis of real world data and thereby estimate the shares of voucher rent that would accrue to buyers and sellers respectively. It results in the conclusion that the scheme would become highly inefficient given the number of vouchers that would have to be issued for HUMN products for rare diseases alone (3-6 per year) and all the more so if they were also issued to reward UMN products for children (5-6 per year). As well as being inefficient, such a scheme, by overloading the market with vouchers, would undermine the efficiency of any future scheme to award vouchers for novel antimicrobials. This class of products would be better adapted to this form of reward as it would entail issuing one – or at most – two vouchers per year.

As well as being costly to public authorities, RDP extension vouchers, by delaying the decrease in the price of those medicines, delay the increase in their uptake, which comes at a price to patients. This effect is measured along with the additional cost to public authorities in the calculations set out below.

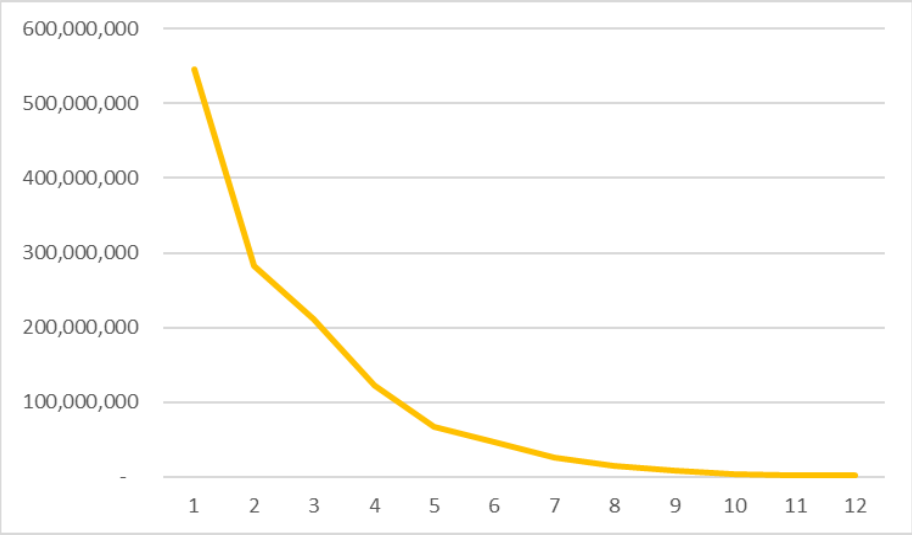
Methodology

The cost to payers and the share of those additional costs that accrues to voucher sellers (i.e. to HUMN originators) is calculated in the following way. First, a representative annual cohort of RDP-protected products is constructed based on IQVIA sales data. This will give the profile of the potential voucher buyers. From this can be inferred the cost of a given annual number of vouchers to public authorities, the share of this expenditure that will go to the intended recipient i.e. the voucher seller, and the cost to patients in the form of lower uptake.

The RDP-protected products with expiry over an 11-year period (2014-2024) were used to construct the representative cohort. First, the medicines are each assigned to their respective annual cohorts. Second, the medicines with expiry in the same year were ranked according to the value of EU sales in the top selling year for each medicine according to IQVIA data. The average peak sales value of the top product from each year group gives the peak year sales value of the top product in the representative sample. The average value of the second product from each year group gives the peak year sales value of the second product in the representative sample and so on.

Table 31 – Peak sales of products in the representative annual cohort

Product	Peak sales
1	545 000 000
2	282 654 545
3	210 890 909
4	122 727 273
5	66 854 997
6	46 362 340
7	25 833 879
8	14 449 938
9	9 270 111
10	3 555 616
11	2 021 996
12	1 807 804



A model based on the decline in revenue experienced by a representative RDP-protected product after protection expiry is used to calculate the cost and benefit to various stakeholders of a one-year exclusivity extension for such a product. Table 32 illustrates the calculation of the value of a

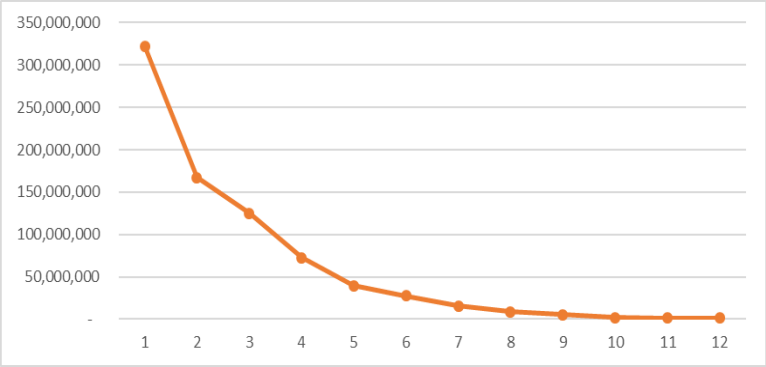
voucher to a voucher buyer, taking as an example the top selling product in the representative cohort.

Table 32 – impact of a voucher on stakeholders, expressed as a percentage of peak year sales of the medicine for which the voucher is bought

	Baseline	Voucher	Change	Change %
Originator sales	981	1063	82	8%
Generic sales	130	100	-30	-23%
Cost to public payer	1111	1163	52	4.7%
Cost of baseline volume	1111	1192	81	7.3%
Patients served	1445	1390	-55	-3.8%
Originator volume	1059	1111	52	
Originator distribution cost	212	222	10	
Net marginal revenue (NMR)	769	841	72	9%
Net present value of NMR			59	

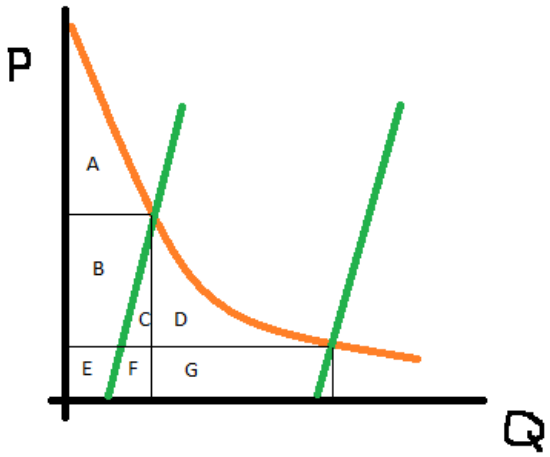
The change in net marginal revenue of the originator (i.e. the voucher buyer) gives the value of the voucher for each buyer and therefore the willingness to pay of each potential buyer. It is thus possible to construct a demand curve for the market for RDP extension vouchers.

Figure 15 – demand function for vouchers



Given this demand function, the supply curve (whose position depends on the HUMN criteria) will determine the equilibrium price.

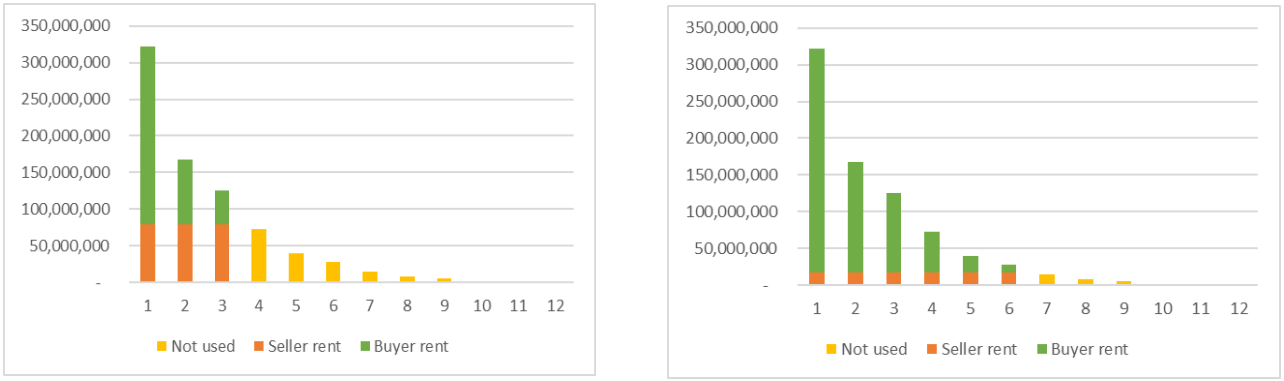
Figure 16 - equilibrium price for vouchers



The supply function can be represented as a vertical line or, arguably, as a steep upward sloping line reflecting the incentive impact of the scheme. Given the shape of the demand curve, the price drops sharply as the number of vouchers increases from one to three to five. In Figure 16 the rent represented by areas B and C go to the voucher seller with a smaller number of vouchers. With a larger number, B and C go to the buyer, along with D. The seller is left with only E, F and G.

In Figure 17 the analysis applied to the representative cohort. Thus, with one voucher issued, the seller's share of the voucher rent is 57%. With three, it is already less than the buyer's share at 39%. With six, it is only 13%, with the remaining 87% wasted on benefits accruing to companies that are not the intended beneficiaries of the scheme.

Figure 17 – The seller and buyer share of voucher rent varies with the number of vouchers



While the originator's revenue increases with a corresponding increase in the expenditure by payers, this is in part offset by a decrease in the revenues of generic manufacturers. However, the implied cost is also an understatement, given that fewer patients will be served over the period considered as a result of higher prices. The cost of the catering to the higher number of patients served in the baseline at the prices seen in the policy scenario is higher.

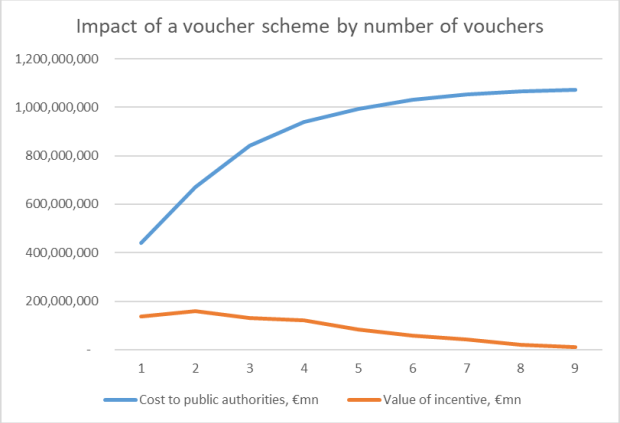
As explained above, there may be up to 6 HUMN medicines for rare diseases per year which would imply the use of six possible vouchers. The matrix below then gives a total annual combined cost to the public payer of **over a billion euros**.

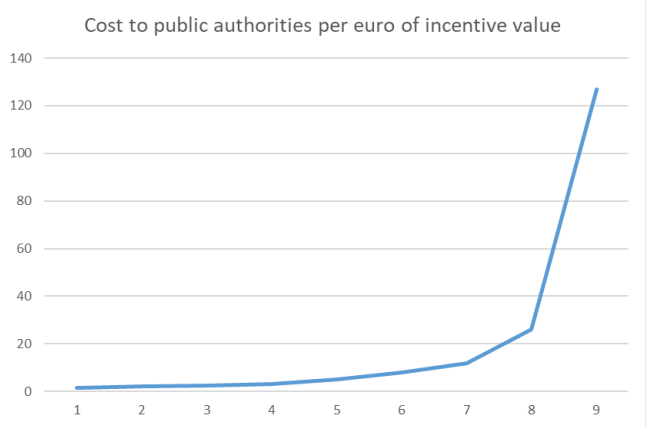
Table 33 – Number of vouchers and financial impact on health systems

# of vouchers	Peak sales	Cost of nth voucher to payers (81% of peak sales)	Cumulative cost to payers
1	545,000,000	441,450,000	441,450,000

2	282,654,545	228,950,182	670,400,182
3	210,890,909	170,821,636	841,221,818
4	122,727,273	99,409,091	940,630,909
5	66,854,997	54,152,548	994,783,457
6	46,362,340	37,553,495	1,032,336,952
7	25,833,879	20,925,442	1,053,262,394
8	14,449,938	11,704,450	1,064,966,844
9	9,270,111	7,508,790	1,072,475,634
10	3,555,616	2,880,049	1,075,355,682
11	2,021,996	1,637,817	1,076,993,499
12	1,807,804	1,464,321	1,078,457,821

Figure 18 – Cost to public authorities per euro of incentive value





A similar analysis has been set out in a paper that appeared in *Health Review* in 2016[227]. Some corroboration of this analysis can be seen from the US experience of issuing priority review vouchers for various classes of products. While a priority review voucher is a distinct mechanism, the effect of the number of vouchers would be similar, as more vouchers would mean that they would be used for less and less revenue-generating products. After what may have been a "teething phase" of the first two, the relationship between the number of vouchers and the price at which they are sold would appear to correspond to the above supply and demand based analysis.

Figure 19 - Number of PRV awarded by FDA

[227] The Commercial Market For Priority Review Vouchers | Health Affairs

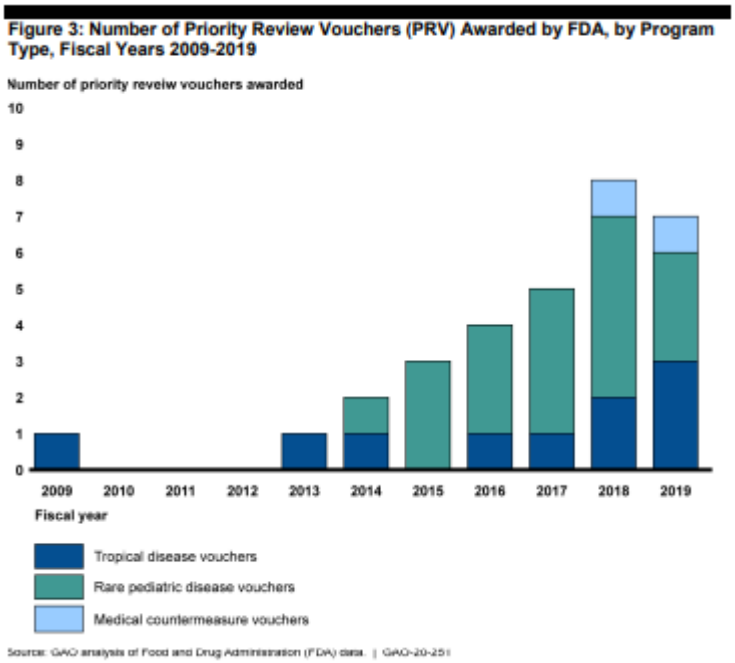
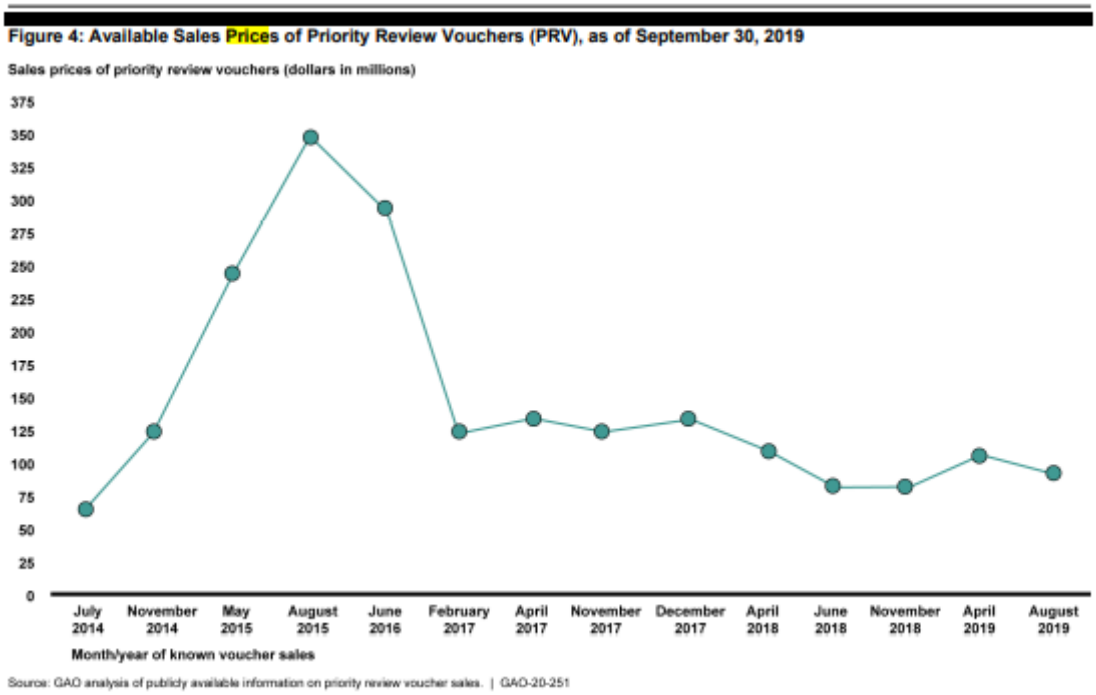


Figure 20: sales price PRV



6. *The impact of measures to improve market access*

The baseline takes account of the preferred option in the revision of the general pharmaceutical legislation, which makes the last year of RDP conditional on authorization in all Member States within two years. However, since orphan medicine originators will benefit from ten years of market exclusivity in the baseline, they will continue to enjoy ten years of protection from generic competition, even if they do not meet the condition. For this reason, Option C for the orphan

revision provides for a conditionality that matches the one that applies to RDP, so that the incentive extends to orphan products that rely on market exclusivity as their last line of protection. Option B, by eliminating market exclusivity has the same effect of allowing the incentive to apply to ME-reliant orphan medicines.

Table 34 - Regulatory protection and market exclusivity periods in different scenarios under Option A

Option A	Not launched in all EU		Launched in all EU		Access premium
	Regulatory protection	Market exclusivity	Regulatory protection	Market exclusivity	
Standard orphan medicines	8 years	**10 years**	9 years	**10 years**	0 year
HUMN orphan medicines	8 years	**10 years**	9 years	**10 years**	0 year

Table 35 - Regulatory protection and market exclusivity periods in different scenarios under Option B

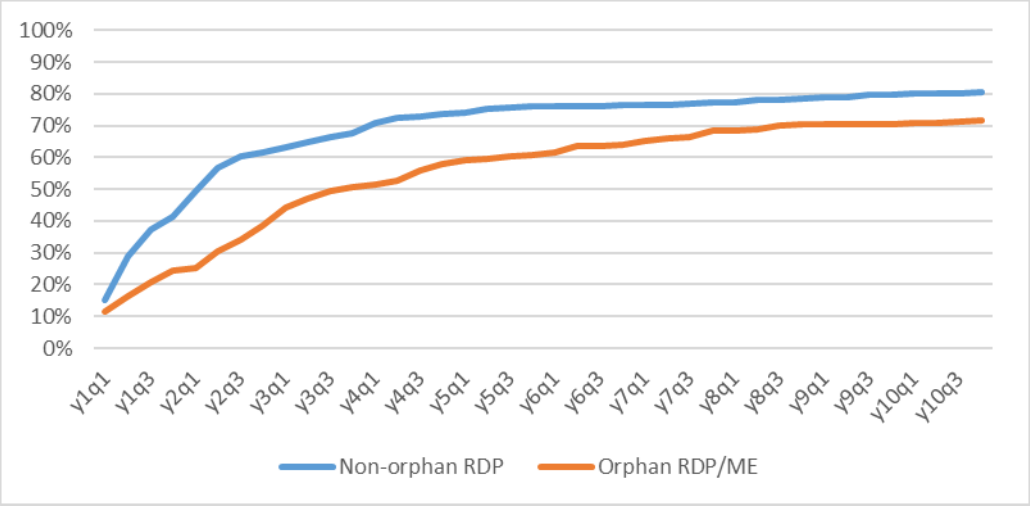
Option B	Not launched in all EU		Launched in all EU		Access premium
	Regulatory protection	Market exclusivity	Regulatory protection	Market exclusivity	
Standard orphan medicines	8 years	**0 years**	9 years	**0 years**	+1 year
HUMN orphan medicines	8 years	**0 years**	9 years	**0 years**	+1 year

Table 36 - Regulatory protection and market exclusivity periods in different scenarios under Option C

Option C	Not launched in all EU		Launched in all EU		Access premium
	Regulatory protection	Market exclusivity	Regulatory protection	Market exclusivity	
Standard orphan medicines	8 years	**8 years**	9 years	**9 years**	+1 year
HUMN orphan medicines	8 years	**10 years**	9 years	**11 years**	+1 year

IQVIA sales data was used to assess the baseline level of access to orphan medicines across 25 Member States[228] for orphan products in the relevant category (reliant on ME rather than SPC). For each molecule and each Member State, the first quarter in which meaningful[229] non-zero sales occurred for at least two successive quarters was taken to indicate the quarter in which the product reached that market. It was then possible to calculate for each products, how many Member States and what percentage of the EU population it had reached after a given number of quarters. Then, taking the average across all the products in the basket, we were able to plot the evolution of the average ME-dependent orphan product and compare it with that of the average RDP-dependent non-orphan product. To follow the evolution of market access over 10 years, the sample was restricted to only those products that are authorised between Q1 2010 and Q4 2011[230].

Figure 21 – Percentage of the EU population having access to the product overtime by protection type



The average ME-reliant orphan can be seen to fare considerably worse than the average RDP-reliant non-orphan. Not only is the final level of access lower, it is achieved more slowly. Deeper analysis point to higher coverage of products with higher sales and that larger member states with higher GDP tend to have a higher share of the products on their market.

Figure 22 – Percentage of population served over time

[228] NB. IQVIA MIDAS sales data were not available for Cyprus and Malta.

[229] At least 1% of the average EU per capita sales volume.

[230] The RDP-reliant non-orphan products in the basket were ABIRATERONE ACETATE, ACETYLSALICYLIC ACID!CLOPIDOGREL, AMLODIPINE!HYDROCHLOROTHIAZIDE!OLMESARTAN MEDOXOMIL, AMLODIPINE!TELMISARTAN, ASENAPINE, BROMFENAC, C1 INHIBITOR (HUMAN), CABAZITAXEL, CLEVIDIPINE, CORIFOLLITROPIN ALFA, DEXAMETHASONE, DEXMEDETOMIDINE, DUTASTERIDE!TAMSULOSIN, GIMERACIL!OTERACIL!TEGAFUR, METFORMIN!SAXAGLIPTIN, PITAVASTATIN, ROFLUMILAST, SILODOSIN, TAPENTADOL, THIOTEPA, VELAGLUCERASE ALFA
The ME-reliant orphan products were ANAGRELIDE, CLOFARABINE, DECITABINE, DEFIBROTIDE, ICATIBANT, MECASERMIN, MIFAMURTIDE, NELARABINE, STIRIPENTOL, TEDUGLUTIDE, THIOTEPA, VELAGLUCERASE ALFA, KETOCONAZOLE, MERCAPTOPURINE

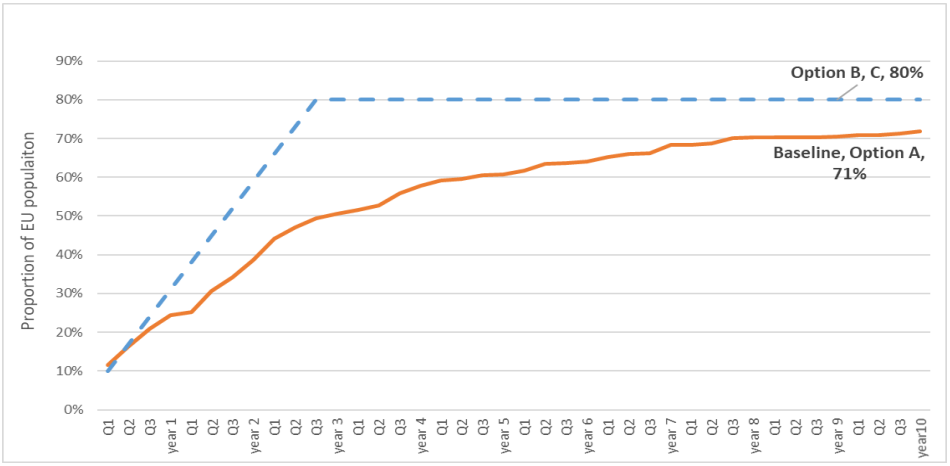


Figure 22 demonstrates the expected impacts of the various policy options on patient access[231]. Option B and C reach a higher plateau of 80% EU population covered, and also much faster than Option A/baseline, two years following authorisation. The maximum achievable access is less than for non-orphan medicines, given the sometimes extremely low or non-existent patient population in Member States. We based our estimation on data from SPC protected orphan medicines, which can reach an average 80% population coverage even in rare conditions, but with higher financial incentives. We assume, that soon after 2 years from authorisation this plateau would be reached, because of the incentive.

7. Medicines for children - Modelling changes in SPC-extension duration

a. Protection types and length in a sample of medicines

In the basket of products from IQVIA database with protection expiry between 2016 and 24, 20% of medicines (40/199) are benefiting either from the +6 months SPC extension (36) or from the two years market exclusivity extension (4) as last protection to expire. These products are highlighted in Figure 6, presented by the length of their overall protection. Importantly, those medicines that are protected by a patent or regulatory protection as a last line of protection (90/199) and not by SPC or market exclusivity, cannot benefit from the reward for carrying out studies in children.

It is important to note that from the IQVIA database it is not possible to determine which products have been studied in children. On the basis of historical data it can be assumed that around 50% of the products under development are granted a full waiver from the obligation of conducting a PIP. By extrapolation, it can be expected that also in the basket considered only 100 of products were subject to the obligation to conduct a PIP. Which brings the percentage of products rewarded with a PIP extension to around 40% of the eligible products.

As explained in the previous section, the number of SPC extensions are smaller than we would expect from the number of new medicines authorised with a PIP obligation, due to a lag in completing PIPs, often many years after authorisation of the adult medicine. Interestingly, medicines with high sales are good at timely completion of the PIPs, we have noted that out of 12 blockbuster medicines (those that have a revenue of €1 billion per year in the EU market) in our basket, 8 had a paediatric extension. In their case, the motivation was high: a 6-month extension generates hundreds

[231] It is hereby important to keep in mind that these incentives work with medicines that are not protected by SPC or patents, as those IP incentives provide longer protection than the maximum achievable market exclusivity for more than half of all newly authorised medicines.

of millions of additional protected revenues. This is reflected in Table 4, those medicines for which the SPC extension is the last layer of protection have longer protection times, and higher average revenues than all the other medicines.

Figure 23 - Distribution of products with paediatric extension by length of protection

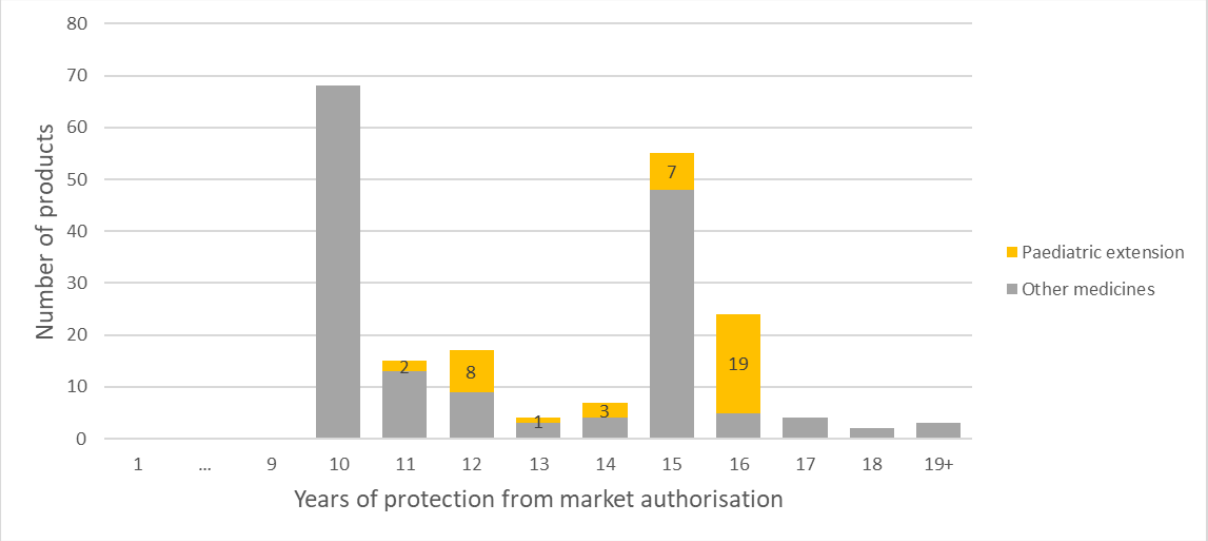


Table 37 - Peak annual sales and protection period of products with paediatric extension

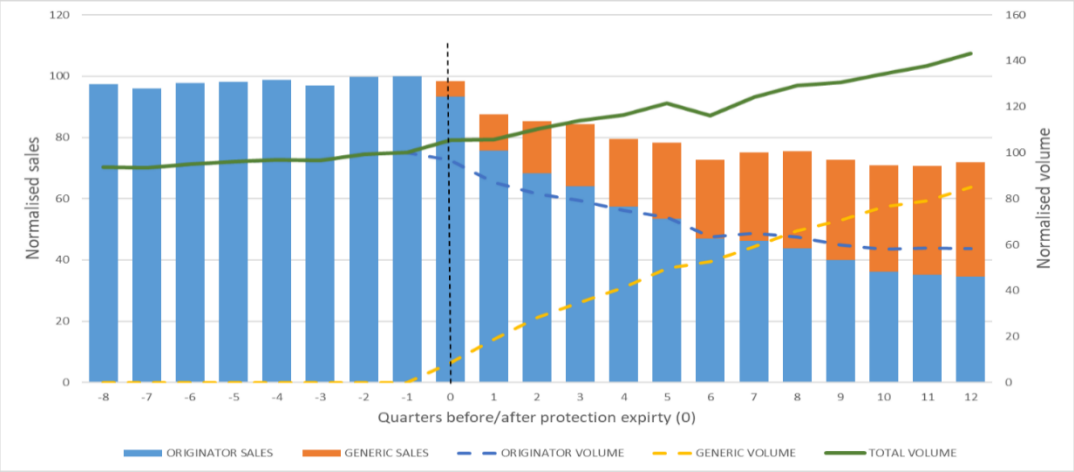
	Avg. peak annual sales	Avg proection period
Paediatric extension	€ 540.6 m	14.3 years
Other medicines	€ 199.5 m	12.7 years

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

To measure the impacts of changes in the SPC extension, we used the same concept as for the general pharma and for the orphan medicines. However, those medicines benefiting from the SPC extension have typically longer protection and generate much higher revenues than the RP protected ones, which serve the basis of the general pharma analogue. The high sales medicines are more prone to generic competition, because of the lucrative market, the generic competitors come faster, in bigger number and with more aggressive price competition.

To properly account for this difference, we built a new analogue based on a different basket of products is used. For this exercise, we considered the 11 products[232] whose SPC protection expired in France, Germany, Italy and Spain between 2016 and 2018 and for which SPC protection is the last line of protection. Since the options concern increases or decreases in protection by six months, quarterly rather than annual data were used.

[232] ADALIMUMAB, BOSENTAN, CASPOFUNGIN, ENTECAVIR, EZETIMIBE, IMATINIB, IVABRADINE, RUPATADINE, TIGECYCLINE, TIOTROPIUM BROMIDE, VORICONAZOLE



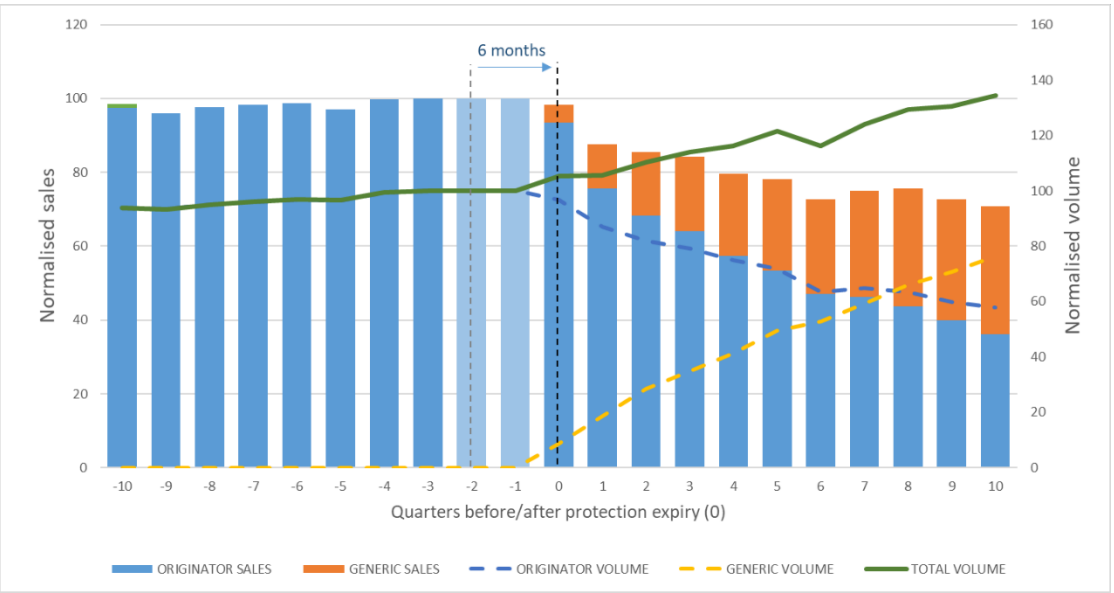
quarter from expiry		-8	-4	-1	0	4	8	12
ORIGINATOR	SALES	97	99	100	93	57	44	35
GENERIC	SALES	0	0	0	5	22	32	37
TOTAL	SALES	97	99	100	98	80	76	72
ORIGINATOR	VOLUME	94	97	100	97	75	63	58
GENERIC	VOLUME	0	0	0	9	41	66	85
TOTAL	VOLUME	94	97	100	105	116	129	143
ORIGINATOR	PRICE	1.04	1.02	1.00	0.97	0.77	0.69	0.59
GENERIC	PRICE				0.56	0.53	0.48	0.44
TOTAL	PRICE	1.04	1.02	1.00	0.93	0.68	0.58	0.50

The analogue indeed confirmed, that for a typical beneficiary of the SPC extension changes from generic entry are more dramatic. 3 years after the expiry, the volume of generic and originator medicines combined has increased by 43% (suggesting 43% more patients being able to benefit from the medicine) and average price halved, compared to quarter -1, the last protected quarter. As in the general pharma, we have modelled changes by moving the expiry point 2 quarters back or ahead within our 21-quarter long observation period.

c. Modelling the economic impact of increasing SPC extension

We use the same data as presented above and assume that after the Q-1 there will be an additional 2 quarters of peak sales protected by a 6-month additional SPC extension. We will use the result of this model to estimate the proportionate effect of the 12-month SPC extension incentive for UMN addressing medicines in Option A. We assume that pre-expiry sales trajectory is unchanged, the market dynamics of generic competition post expiry is unchanged. In the figure below thus data associated with a new Q-1 is added twice and the baseline Q11 and 12 are removed to maintain the overall observation period of 21 quarters. Figure X

Figure 24 - Normalised volume and sales data for products with +2 quarters of SPC extension



	Baseline	12-month SPC ext	change
Originator protected sales	785	985	**+200**
Originator contested sales	695	625	**-70**
Originator gross profit	975	1101	**+125**
Generic sales	327	254	**-73**
Generic gross profit	108	84	**-24**
Cost to public payer	1807	1865	**+58**
Volume (patients served)	2360	2278	**-81**
Cost of baseline volume	1807	1923	116

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

Using the above model for the product lifetime, we can make the following observations at product level:

- Originator companies increase pre-expiry sales due to additional 6 months of monopoly sales by 200 (normalised units). In terms of gross profit, this is 125 more normalised unit.
- Generic companies' start to benefit from sales 2 quarters later, and thus generic sales are reduced by 73 (normalised units), and gross profit is reduced by 24 (normalised unit) compared to the baseline.
- Healthcare payers pay more overall due to an increase in the average price they need to pay for a standard unit of the product. The total cost for healthcare payers is thus +58 (normalised units) over the product lifetime compared to baseline
- Patients lose -81 (normalised units) in decreased volumes of the medicine over the lifetime of the product compared to baseline.

i. Monetising the systemic effects of 12-month SPC extension for medicines addressing UMN (Option A)

We expect that 20% of the new products will meet the UMN criteria, therefore out of the expected yearly 10 SPC extension, 2 would be for UMN addressing medicine. Increasing the current 6-month

SPC extension to 12 for these medicines would result in the following impacts, by using the changes values of the models and the value of €540 m peak annual sales, derived from historic data.

Table 38 - Impact of 6 months protection increase (+12 months SPC extension) for UMN on different stakeholders

	avg product (€540 m annual sales)	Systemic impact (2 extensions/year)
Originator gross profit	**+€169 m**	**+€338 m**
Generic gross profit	-€32 m	-€64 m
Public payer's gain/loss (cash)	-€78 m	-€156 m
Δ of patients treated (monetised)	-€78 m	-€156 m
Patient and payer gain/loss	**-€156 m**	**-€312 m**

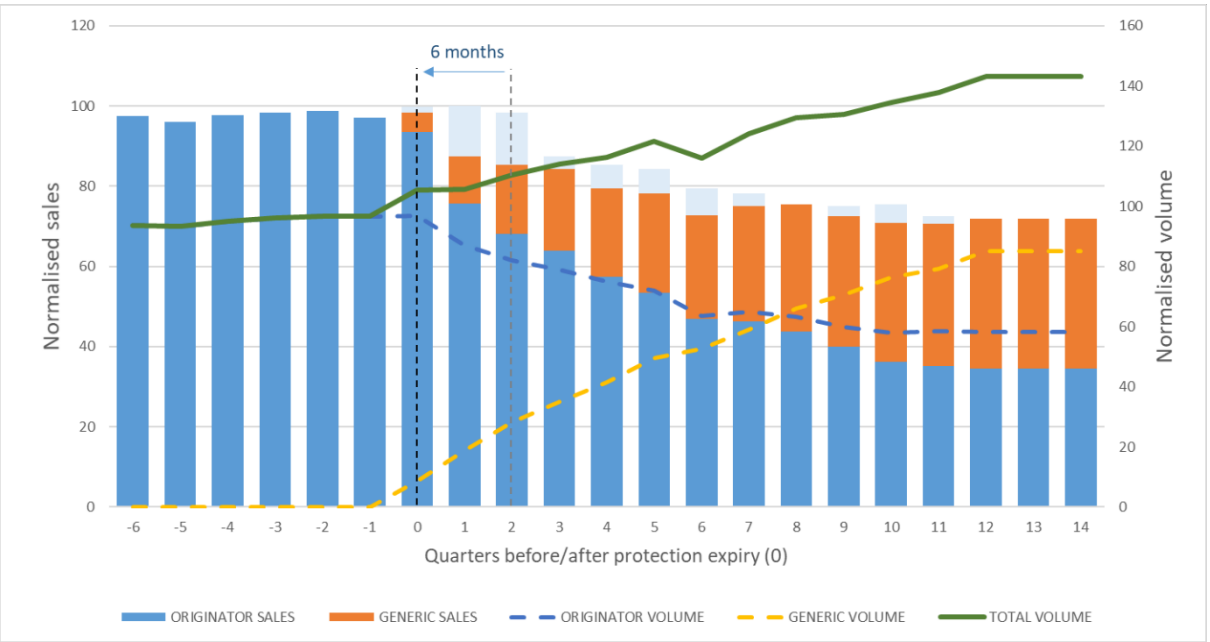
Thus, benefiting originator companies would increase profits by €338 m at a cost of €312 m to the public. Generic companies would experience a €64 m decrease in their gross profits.

d. Modelling the economic impact of decreasing SPC extension

Option B would abolish SPC extension reward, thus reducing protection by 6 months compared to the baseline. This will be the new scenario for the analogue. In the model, we assume that after 3 full years of generic competition an equilibrium value of annual sales and volume of product sold are established and thus we can use Q12 data for originator and generic products as long-term level to calculate the value of ME loss over the product lifetime.

We also assume that the pre-expiry sales trajectory is not changed by company behaviour and thus the baseline Q-1 and Q-2 sales are lost under the new regime. In the figure below thus the original Q-1 and Q-2 values are removed and Q13 and Q14 values are added at equilibrium level. In addition, we assume that the market dynamics of generic competition (between Q0 and Q12) in the new regime will not change compared with the baseline 6-month SPC extension.

Figure 25 - Normalised volume and sales data for products with -2 quarters of SPC extension



	Baseline	No SPC	change
Originator protected sales	785	585	**-200**
Originator contested sales	695	764	**+69**
Originator gross profit	975	850	**-125**
Generic sales	327	402	**+75**
Generic gross profit	108	133	**+25**
Cost to public payer	1807	1751	**-56**
Volume (patients served)	2360	2447	**+87**
Cost of baseline volume	1807	1695	-112

Using the above model we can make the following observations at product level:

- Originator companies' pre-expiry sales loss of -200 (normalised units) translates to a decrease in originator's gross profit of -125 (normalised units) over the observed 21-quarter period.

  We know that pharmaceutical industry is one of the most R&D intensive sector and they reinvest a large share of their revenue into innovation for new products and technologies. This share is 20% on average globally[233] and we can assume that the revenue loss will translate to a loss of innovation budget.

- Generic companies' start to benefit from sales half year earlier compared to baseline, and thus reach equilibrium level 2 quarters earlier. These two extra quarters of equilibrium generic sales of +75 (normalised units) are equal to +25 (normalised units) gross profit gains.
- Healthcare payers pay less overall due to a decrease in the average price they need to pay for a standard unit of the product. In the baseline +6 months SPC extension regime, the total lifetime

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

sales is 1807 (normalised units) and in the new 8-year protection regime the same volume at the new prices would be 1756 (normalised units). Thus in the new situation healthcare payers would pay 56 (normalised units) less.

In the real situation, however, healthcare payers may not realise this nominal saving but choose to purchase more units of the medicine at a lower price for the healthcare system and expand coverage of patients. The difference in the cost of the baseline volume (at new prices) contains both the decreased payment and the extra volumes, so the joint gain for the public is 112 (normalised unit).

- Patients benefit due to the increased volume of the medicine sold after protection expiry (6 months earlier) which then reach more patients creating higher level of health benefits. In the model, the total volume increases as soon as generic products enter the market and volume of generic products surpasses that of the originator product by year 4 after generic entry. In the new regime the total volume sold increases by +87 (normalised units).

i. Monetising the systemic effects of abolishing SPC extension (Option B)

Under option B, medicines which would currently be eligible for the 6-months SPC extension will lose such protection. Generic medicines could enter the market earlier and public authorities would pay less, for more patients served. We have adjusted our model to the new expiry and compared it to the baseline. Table 38 shows the impact of the change for all stakeholders, both at an individual product level, and at systemic level for all 10 products, that would benefit from the extension in the baseline.

Table 39 - Impact of 6 months protection reduction on different stakeholders

	avg product (€540 m annual sales)	Systemic impact (10 extensions/year)
Originator gross profit	**-€169 m**	**-€1,690 m**
Generic gross profit	+€33 m	+€330 m
Public payer's gain/loss	+€76 m	+€760 m
Δ of patients treated (monetised)	+€75 m	+€750 m
Patient and payer gain/loss	**+€151 m**	**+€1,510 m**

At an individual product level, the reduction is a significant loss to the **originator company**, an average SPC extended product would lose -€169 m gross profit. The **generic** products would have +€33 m higher profits thanks to the earlier entry. The **public payer** would experience +€76 m yearly savings, however this is not the only benefit for the public. Not only the total cost would be less, but more **patients** could be served with the more affordable medicine, adding an additional +€75 m monetised patient benefit. Overall the public gains €151 m thanks to the reduction. Looking at systemic level, the loss of 10 SPC extensions compared to the baseline would cause €1.690 m profit loss to the innovator industry annually. On the other hand, the public would make significant savings, to the tune of €1,510 m per year.

e. Cost of a PIP

Building on data reported in the Joint Evaluation Table 7, which provides the probability that each cost is incurred during the conduction of a PIP, it has been estimated the average administrative (0.5 M€) and R&D (22.2 M€) costs of a completed PIP.

TABLE 40 - Estimated costs of a PIP

Estimated costs of a PIP broken down to stages	*est. avg cost of a PIP stage (EURO)*	*Estimated to happen in PIPs*	*est. avg cost of a completed PIP (EURO)*
Preparation of the initial PIP application	400,000	100%	400,000
Annual reporting and further PIP modifications	100,000	55%	55,000
Other administrative costs	200,000	42%	84,000
estimated AVG administrative cost per completed PIP			**539,000**
In vitro studies and animal studies	800,000	40%	320,000
Development of a paediatric formulation	1,600,000	47%	752,000
Phase II paediatric clinical trials	7,300,000	48%	3,504,000
Phase III paediatric clinical trials	15,700,000	72%	11,304,000
Other R&D costs	14,400,000	44%	6,336,000
estimated AVG R&D cost per completed PIP			**22,216,000**

Source: calculation on data collected from the Joint Evaluation

To estimate the total administrative costs incurred yearly by industries, we have multiplied the number of PIPs completed per year with the estimated AVG administrative cost per completed PIP (539 k€).

The completion of a PIP requires time, the analysis – conducted on 205 pMPs with a PIPs agreed during 2007-2020 – of the time needed to obtain a market authorisation (MA) for the paediatric indication after the completion of the PIP, identified an average time of 5.3 years – rounded to 5 - from the first EMA opinion to the MA date[234] (information on both dates are available for 119 of the 205 pMPs, 58%), in line with the 7 years of the "average planned duration of a PIP, from the date of initial application to the planned completion date" reported in the Joint Evaluation. Therefore, it was assumed that R&D costs of a PIP (22.2 M€) are equally distributed over the 5-year period preceding the MA (year of obtainment included) to estimate the total R&D costs incurred yearly by industries

ANNEX 5: HOW OPTIONS ARE EXPECTED TO CONTRIBUTE TO THE ACHIEVEMENT OF THE OBJECTIVES

1. Options for rare diseases

Objective	Common elements	PO A	PO B	PO C[235]

[234] It has been observed that "*The median time to the composite endpoint of first results reporting (either in a trial registry or peer-reviewed journal) was 4.7 years (IQR 3.2 to 5.8 years) from the date of publication of the PIP*" [Hwang, T. J., Tomasi, P. A., & Bourgeois, F. T. (2018). Delays in completion and results reporting of clinical trials under the Paediatric Regulation in the European Union: A cohort study. PLoS medicine, 15(3), e1002520. https://doi.org/10.1371/journal.pmed.1002520].

[235] All the options (PO A, PO B and PO C) include also common elements. Common elements are presented separately only once to facilitate presentation and avoid repetitions.

1. Foster innovation and investment in research and development of medicines for rare diseases and for children especially in areas of (high) unmet medical need	Criteria to identify products addressing HUMN will be set in the Orphan Regulation. Products addressing HUMN will be entitled to increased scientific support by the Agency. *These measures are expected to facilitate the development and faster development of products addressing HUMN*	10 years of market exclusivity (ME) + transferable regulatory protection voucher for HUMN products *The 10–year market exclusivity (the same for all orphan products categories) will foster the development of research into orphans in general, hence contributing to innovation. It is the transferrable regulatory protection voucher (granted to products addressing HUMN) which is expected to foster research into HUMN (and hence also more targeted innovation)*		Variable duration of the ME: 10 years of ME for HUMN products; 9 years of ME for new active substances; 5 years of ME for well-established use products. *While the market exclusivity targets all orphan products, a modulated duration of ME will better direct research into HUMN and into new active substances.*
2. Create a more balanced and competitive system that keeps medicines affordable for health systems and patients while rewarding innovation	Generics/biosimilars can enter the market at day-1 of the expiry of the exclusivity period by allowing the filing of an application prior to expiry. *This measures aims at a faster entry of cheaper generics (affordability), which at the moment is delayed by the time needed from filing of the application until granting an authorisation (120 days). At the same time, the measure does not impact innovation, as the ME period remains intact.* Reduction of consecutive periods of market exclusivity for new indications of the same orphan medicine by introducing them under the same "Global Marketing Authorisation" (GMA). *This measure, by proving the extension of ME for only two first new indications, will allow (cheaper) generics to enter*		No ME *No ME exclusivity will ease the entry of generics, but at the same time, it may be questioned whether innovation will be sufficiently rewarded.*	Variable duration of the ME *This measure will create a more balanced system where especially innovation and addressing HUMN is rewarded. Authorisation of orphan products with well-established use will still be rewarded (as it is important to have products officially authorised for a specific use on the market), but with a shorter 5-year ME. Variable duration of ME will help faster entry of generics (to address affordability).*

	faster the market (affordability). At the same time, it creates a better balance between the need to reward innovation (while avoiding unjustified benefitting from the system|) and the need for a fast generics entry, The market exclusivity granted to a second generation product that is similar to the first generation product shall not be applied in respect of generic products of the first reference product for which the market exclusivity expired. *As above, this measure preserves innovation and blocks the unjustified benefiting from the system of incentives ('evergreening'), while allowing a faster entry of generics (affordability).*			
3. Enable timely patient access to orphan and paediatric medicines in all Member States	Generics/biosimilars can enter the market at day-1 of the expiry of the exclusivity period by allowing the filing of an application prior to expiry. *This measure ensures timely access of generics. See also explanations for this measure in point 2.* Reduction of consecutive periods of market exclusivity for new indications of the same orphan medicine by introducing them under the same "Global Marketing Authorisation" (GMA). *This measure*			Extension of the ME if market launch in all EU Member States (for HUMN products and new active substances). *This measure awards those companies which made efforts to reach out to all MS, even those where marketing products is less attractive for companies (due to limited public funds to buy expensive medicines, small markets, etc.)*

	ensures timely access generics. See also explanations for this measure in point 2. . The market exclusivity granted to a second generation product that is similar to the first generation product shall not be applied in respect of generic products of the first reference product for which the market exclusivity expired. *This measure ensures timely access generics. See also explanations for this measure in point 2.* Encourage companies that lose the commercial interest in an orphan medicine to offer it for transfer to another company rather than withdrawing it *This measure will help patients' access to a medicine which risks withdrawal from the market.* The duration of the orphan designation (assigned early in the development of a product and prior to obtaining a marketing authorisation) will be capped for newly designated orphan medicinal products at 7 years. *This measure is expected to motivate the sponsor to timely develop the product and as a result it helps timely patients' access.*			
4. Reduce the regulatory burden and provide a flexible regulatory framework.	Provide for the possibility to adapt the current definition of an orphan condition *This measure opens up the possibility that the current*			

	definition of an orphan condition may be easier adapted (for example to scientific developments). The orphan designation criterion on the basis of return on investment will be deleted. *This measure 'cleans up' a criterion to get an orphan designation that has become obsolete.* Responsibility for adopting decisions on 'orphan designations' will be transferred from the Commission to the Agency. *This measure will facilitate and expedite the procedure, as the same body (Agency) will be responsible for a scientific opinion and for an orphan designation (while currently the Commission gives the decision on an orphan designation).*			

Further explanation of important parts of the common elements:

- ***Global marketing authorisation*** (*Reduction of consecutive periods of market exclusivity for new indications of the same orphan medicine by introducing them under the same "Global Marketing Authorisation" (GMA).*

'Global marketing authorisation' is a concept which exists already under Directive 2001/83/EC (Article 6(1)) and means that a medicinal product has been granted a marketing authorisation, any additional strengths, pharmaceutical forms, administration routes, presentations, as well as any variations and extensions shall also be granted an authorisation in accordance with the first subparagraph or be included in the initial marketing authorisation. All these marketing authorisations shall be considered as belonging to the same global marketing authorisation. A measure proposed in this IA under the Orphan Regulation uses the same concept, but for the purpose of indications as one medicinal product may have a several indications (an indication means a medical condition that a medicine is used for. This can include the treatment, prevention and

diagnosis of a disease[236]). An indication should clearly state the disease/condition and population that a medicine is intended to treat. What is taken into account is severity of the disease, the place in the therapy, e.g. 1st, 2nd line, use in the combination therapy and other[237]. As these indications may be formulated narrowly, the measure of reduction of ME, which would be granted only for two indications, prevents drawing unjustified benefit from the ME.

- ***Transfer of the orphan marketing authorisation*** (*Encourage companies that lose the commercial interest in an orphan medicine to offer it for transfer to another company rather than withdrawing it*)

At the moment companies which lose the commercial interest in an orphan medicine may withdraw it from the market with no regulatory consequences, while generic products will not necessarily be interested to fill in the gap, either (rare diseases are characterised by very small patient populations). Even if another company would be willing to take over, the fact of withdrawal may be not sufficiently publicised and other forms of encouragement not provided.

- ***Duration of orphan designation*** (*The duration of the orphan designation (assigned early in the development of a product and prior to obtaining a marketing authorisation) will be capped for newly designated orphan medicinal products at 7 years)*

Currently, the orphan designation once granted is not limited in time. There may be situations where the orphan designation is lost (see Article 5 (12) of the Orphan Regulation)[238], but the lapse of time is not one of them. Several orphan designations may be introduced to the Register of Orphan Medicinal Products for the same condition, all of them entitled to pre-authorisation scientific and procedural facilitations, so one designation does not block research on other products. However, as the ultimate purpose is to deliver the product to the patient, companies should be encouraged to swiftly proceed to the marketing authorisation stage. The overpopulation of the Register with 'old' designations is also not good for its readability. As the average time the average time between orphan designation and MA Application (MAA) is 5 years, a somehow longer period of seven years, was suggested for a cap.

- ***Designation procedure*** (*Responsibility for adopting decisions on 'orphan designations' will be transferred from the Commission to the Agency.)*

The procedure for designation is set out in Article 5 of the Orphan Regulation. The applications for orphan designation are examined by the EMA's Committee for Orphan Medicinal Products (COMP), using the network of experts that the Committee has built up. The evaluation process takes a maximum of 90 days from validation. The Agency sends the COMP opinion to the European Commission, which is responsible for adopting a decision on the orphan designation within 30 days of receipt of the opinion. The full list of orphan designations is available in the Community register of orphan medicinal products for human use, managed by the Commission. In the proposed change, the responsibility for adopting decisions would be transferred to the Agency, which is expected not make the procedure faster and less burdensome.

[236] Indication | European Medicines Agency (europa.eu)
[237] Wording of therapeutic indication - guide for assessors (europa.eu)
[238] (a) at the request of the sponsor; (b) if it is established before the market authorisation is granted that the criteria laid down in Article 3 are no longer met in respect of the medicinal product concerned; (c) at the end of the period of market exclusivity as laid down in Article 8.

2. Options for medicines for children

Objective	Elements common to all PO	PO A (SPC extension and novel incentives for UMN products)	PO B (No SPC extension)	PO C[239] (6 months SPC extension)
1. Foster innovation and investment in research and development of medicines for rare diseases and for children especially in areas of unmet need.	Criteria to identify products which have the potential to address unmet medical need of children will be defined in the general pharmaceutical legislation. Products which respond to these criteria will be entitled to increased scientific support by the Agency in the early phases of development this will help the development of novel products for children in areas of UMN. This measure is expected to benefit in particular SME who have more limited resources than big pharma companies Review of the waiver system to take into account the mechanism of action of a product: For products which, on the basis of scientific evidence on the mechanism of action, could also be effective against a different disease in children, clinical studies in children will have to be conducted. This will results in novel products for children in particular in areas in areas of UMN The new procedural system will allow for evolutionary PIP, which will help accommodate innovation	Novel incentives for UMN products. alternatively: A regulatory protection voucher (duration 1 year) or an extra 12 extra months SPC extension (on top pf 6 months' extension for all medicinal products) The novel incentives are expected to support the development of novel products for children in the areas of UMN		
2. Create a more balanced and competitive system that keeps medicines affordable for health	Abolishing the market exclusivity extension for completing PIPs would regulate a system that is not functioning well and		The abolition of the SPC extension will allow earlier generic entry and consequently	

[239] All the options (POA, POB and POC) include also common elements. Common elements are presented separately only to facilitate presentation and avoid repetitions.

systems and patients while rewarding innovation ;	will allow predictability for generic products and faster entry of generics in cases where products are not orphan medicines (which in turn will affordability due to lower prices of generics)		improve affordability for the health systems	
3. Enable timely patient access to orphan and paediatric medicines in all Member States;	Cap the duration of the deferrals to 5 years allowing faster development of medicines for children and consequently a higher access to them. The procedure for setting out a PIP will be streamlined and simplified allowing for quicker completion of the PIP and faster authorisation allowing a faster access to new medicines for children Abolishing the market exclusivity extension for completing PIPs would regulate a system that is not functioning well and will allow predictability for generic products and faster entry of generics in cases where products are not orphan medicines		No SPC extension will ensure a faster access to generic product	
4. Reduce the regulatory burden and provide a flexible regulatory framework.	Introduction of an evolutionary PIP model for specific paediatric developments Introduction of an simplified PIP model for specific paediatric developments) These measures are expected in resulting in reduced administrative costs for companies.			

Common elements:

- *Evolutionary PIP*

In the current legislation a complete development plan needs to be submitted to the Agency and agreed with at very early stage of development (after the completion of the pharmacokinetic and pharmacodynamics studies). For certain type of development this is problematic. For example when a molecules have never been used before, the detailed design of the each step of clinical development depends from the results obtained in the previous studies. The obligation to submit a full development plan at early stages obliges developers to make assumptions on the results that will be obtained in the future and results in subsequent need to modify the development plan (PIP) several times. This create delays in the completion of the PIP and administrative burden for the applicants and for the Agency.

With the concept of evolutionary PIP, certain type of developments, like molecules used for the first type in human, will be given the possibility to present a high level clinical development plan. The Agency will agree that the development plan will be completed and new information submitted and agreed at precise development steps. This will reduce the administrative burden and create when necessary a more agile PIP system.

- *Simplified PIP*

The PIP system has been put in place taking into account the development of products for adults for which a clinical development in children derives from the obligation imposed by the legislation.

However, there are cases, like paediatric only products or PUMA products which are developed specifically for children and would therefore be developed indipendedly from the paediatric Regulation. For these products the binding elements and the details that have to be presented in a PIP can be lowered. Specific guidelines on the elements that will be requested for this category of products will be determined by the Agency in close collaboration with interested stakeholders and the Commission.

- *Changes to the waiver system to take into account the mechanism of action of a product*

Currently, the obligation to conduct a PIP in children is waived in certain situation, for example when an adult product is intended for a disease not existing in children.

However, in certain cases the molecule in question, due to its molecular mechanism of action may be efficacious against a disease in children different from the one for which it was initially designed for use by adults. For example a product developed to treat an adult cancer, non-existing in children, could also be effective to treat a different type of cancer in children.

The waiver system is intended to be amended in order to oblige the conduct of PIP also when on the basis of the molecule of action of the product, it may treat a different disease in children.

A similar system has recently been introduced in the US[240].

- *Cap to the length of deferrals*

While the paediatric legislation foresees that clinical studies in children should be completed before the marketing authorisation in adult is granted, there is the possibility *to defer* the completion of some PIP studies only after the marketing authorisation of an adult product. It is envisaged to cap the maximum length of this derogation to 5 years, so that products reach children quicker than today.

- *Abolish the paediatric market exclusivity extension*

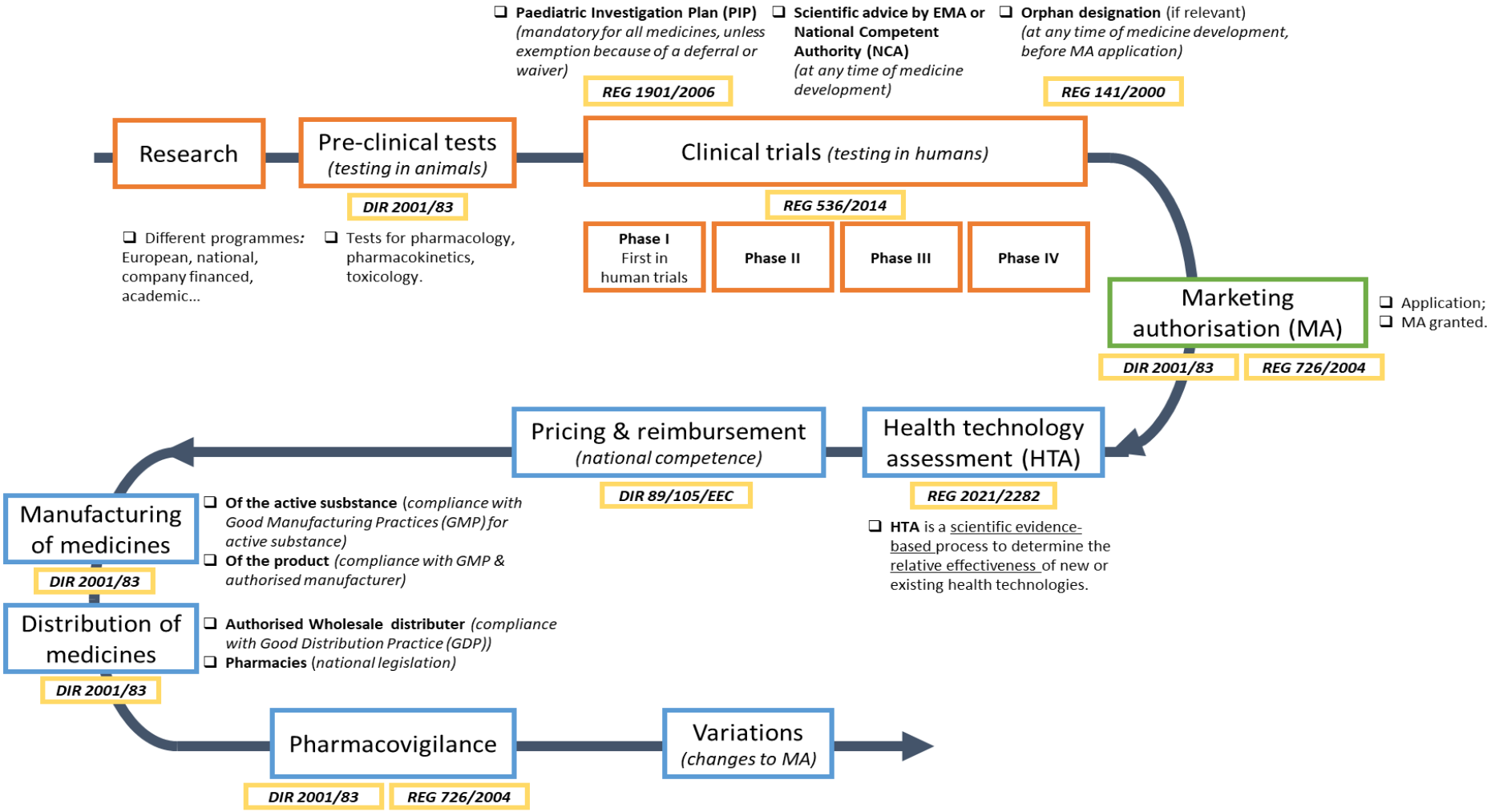
This measure intends to regulate a dysfunctional system. Currently the paediatric regulation offers 6 months SPC extension for completing PIP, and for orphan medicines 2 years of market exclusivity extension. From the entry into force of the Paediatric Regulation up to 2020, only 11 of these market exclusivity extensions were granted. The system has allowed some companies to game the system: there have been cases where companies have abandoned the orphan status of their product at the moment of marketing authorisation in order to benefit from the 6 months SPC extension. This has made difficult for generic products to know exactly when the paediatric protection would expire and consequently to plan accordingly.

- *Facilitations for products addressing UMN*

[240] Download (fda.gov)

Criteria to identify products which have the potential to address unmet medical need of children will be defined in the general pharmaceutical legislation. Products which respond to these criteria will be entitled to increased scientific support by the Agency in the early phases of development and dedicated funding.

ANNEX 6: VISUAL OVERVIEW OF THE LIFE-CYCLE OF A MEDICINAL PRODUCT INCLUDING LINKS TO LEGAL FRAMEWORK



ANNEX 7: OVERVIEW OF ECOSYSTEM AND LEGAL FRAMEWORK

1. The pharmaceutical ecosystem

1.1. General

The Pharmaceutical Strategy for Europe[241] describes the pharmaceutical ecosystem and changes in the landscape that transform industry and medicines development from the old model of chemical blockbuster medicines to biological medicines, advanced therapy medicines, combined medicines with software and personalised medicines. Health data is key to fully exploiting the huge potential of new technologies and digitisation. This vision is echoed in the health ecosystem of the updated European industrial strategy[242].

The EU pharmaceutical ecosystem covers activities from pre-clinical research to manufacturing and includes actors ranging from manufacturers (including medical devices and equipment and personal protective equipment), healthcare services; health tech and related services[243]. Overall, it covers **24.8 million direct jobs**, **493 000 firms** (including 99.7% SMEs) and contributes to **9.5% of EU value added**[244]. The EU provides an attractive market for the pharmaceutical industry, especially with regards to the activities and support provided by the European Medicines Agency and the EU-wide marketing authorisation. These elements are key in attracting R&D to the EU and are regulated by the general pharmaceutical legislation. At global level, the EU health industries are also key players in competition with North America and Asia. As an example, in 2018, North America accounted for 48.9% of global sales of medicines compared to Europe (incl. Switzerland) accounting for 23.2%. The EU also accounts for 24% of the world's API production compared to 65.5% being produced in Asia Pacific. The EU pioneered in sophisticated biologic innovative medicines (and biosimilar medicines), however, Asia and the US are rapidly catching up[245].

In the ecosystem, 'big pharma'[246] are increasingly outsoucing functions, including clinical trials and manufacturing, and are focusing investment on a limited number of therapeutic areas while disinvesting from others[247]. Emerging biopharma companies – often SMEs – are driving a large portion of innovation and development. Emerging biopharma companies were responsible for a record 65% of the molecules in the R&D pipeline in 2021, up from less than 50% in 2016 and 33% in 2001. Top pharmaceutical companies' share of the total R&D pipeline has been shrinking over the last decade (PharmaProjects 2020).

Big pharma is increasingly disinvesting from risker upstream research and instead access products that are already in later clinical trials stages through acquisitions of small biotech

[241] COM(2020) 761 final.
[242] COM(2021) 350 final European industrial strategy | European Commission (europa.eu).
[243] SWD(2021) 351 final – page 138.
[244] SWD(2021) 351 final – page 137.
[245] SWD(2021)351 final – page 139.
[246] Understood as multinational companies dominating the industry sales and traditionally responsible for all aspects of the medicines discovery pipeline.
[247] European pharmaceutical research and development. STUDY Panel for the Future of Science and Technology. European Parliament Research Service.

companies or start-ups with promising portfolios of patents[248]. Once the molecule reaches a certain maturity (e.g. completing phase II clinical trials) and still looks commercially promising, big pharma companies come in, they partner, buy the molecule or buy the company at the stage of the expensive late-stage clinical trials, marketing authorisation and market launch. Licensing is also used extensively in the pharmaceutical sector, though small firms and start-ups also rely on venture capital to finance their R&D (Kyle 2020).

2. Legal framework

a. Basic legislative acts

The **general EU pharmaceutical legislation** consists of Directive 2001/83/EC and Regulation (EU) No 726/2004 forming one policy intervention. Directive 2001/83/EC provides the framework for authorisation and monitoring of medicines post-authorisation (pharmacovigilance) for nationally authorised medicines, manufacturing and wholesale distribution and authorisation of actors in the supply chain, advertising and falsified medicines. The Regulation establishes the European Medicines Agency and its governance and provides also the framework for authorisation of medicines through a centralised procedure and for pharmacovigilance of these medicines. When it comes to technical requirements for the authorisation application and the lifecycle management of medicines, the Regulation refers regularly to the common requirements in Directive 2001/83/EC.

Medicines may either be authorised centrally by the Commission based on a positive scientific assessment by the European Medicines Agency (EMA), the centralised procedure (CP), or nationally by an individual or a group of Member States. A medicinal product authorised via the CP is not necessarily accessible in all Member States, as its actual placing on the market may depend on the launch strategy of companies and national pricing and reimbursement decisions. Both legal acts are grounded on the fundamental principle that a medicine for human use may only be placed on the market once authorised based on a positive benefit-risk of its quality, safety and efficacy, and that applies regardless of the authorisation procedure.

The specialised legislations for rare diseases and children ("the Orphan and Paediatric Regulations") complement the general EU pharmaceutical legislation (that also apply to medicines for rare diseases and children) to specifically support the development in these previously neglected areas, mainly through specific, additional incentives and obligations. Both the Orphan and Paediatric Regulations are designed to address specific unmet medical

[248] European pharmaceutical research and development. STUDY Panel for the Future of Science and Technology. European Parliament Research Service.

needs of small populations: (i) the Orphan Regulation aims at enabling research, development and authorisation of new medicines for rare diseases through specific incentives and (ii) the Paediatric Regulation works mainly with obligations. It compels companies already developing products for adults to screen them for possible use in children. It provides rewards once this obligation has been fulfilled, to compensate for the additional costs.

The revision of these specialised legislations, also ongoing, follows coherent objectives with the revision of the general pharmaceutical legislation: promoting innovation to better address unmet medical needs, ensuring access of patients to innovative medicines and reducing regulatory burden. Taken together, they aim to ensure the right balance between giving incentives for innovation to strengthen the research base of the EU pharmaceutical industry and the need for patients to have access to affordable medicines.

Advanced therapy medicines[249] are also regulated under specialised legislation. This legislation is also an 'add-on' the general pharmaceutical legislation for this specific product category and concerns in particular technical requirements adapted to the particular characteristics of these products, special incentives for SMEs and their assessment. The legislation on advanced therapy medicines is not subject to revision and as such not in the scope of this impact assessment.

These legislations are complemented by more specific ones, applicable at different stages of the lifecycle of medicines.

b. Other legislative acts and policies applicable to medicinal products

i. At the research and development stage

The Regulation on clinical trials[28] harmonises the processes for the assessment and supervision of clinical trials throughout the EU. The evaluation, authorisation and supervision of clinical trials are the responsibilities of Member States and the Regulation ensures harmonisation. The regulation also allows as of 2022 a more efficient process for the approval of multinational trials. Having a single application and a single package will streamline the registration, assessment and supervision processes for EU clinical trials. This will also facilitate the conduct of trials in small populations scattered in several countries.

[249] Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004, OJ L 321, 10.12.2007, p. 121, LexUriServ.do (europa.eu).

The **proposed Regulation on the European Health Data Space** (EHDS)[250] will provide a common framework across EU Member States for access to quality health data for use in research and development of new treatments.

The **European innovation Council** (EIC)[251] established under the Horizon 2020 programme aims at identifying and supporting breakthrough technologies and game changing innovations with the potential to scale up internationally and become market leaders. It supports all stages of innovation from R&D on the scientific underpinnings of breakthrough technologies, to validation and demonstration of breakthrough technologies and innovations to meet real world needs, to the development and scaling up of start-ups and small and medium-sized enterprises (SMEs).

The **Innovative Health Initiative Joint Undertaking**[252] (IHI JU) is a public-private partnership between the European Union, represented by the European Commission, and several health industries from the biopharmaceutical, biotechnology and medical technology sectors. IHI brings together diverse stakeholders (universities, companies large and small, and other health stakeholders) in collaborative projects that address disease areas where there is a high burden on patients and/or society. The initiative focuses on cross-sectoral projects supporting the development of safe, effective, people-centred and cost-effective products and services that target key unmet public health needs.

ii. At the authorisation stage

The authorisation procedures are laid down in the general pharmaceutical legislation but aspects linked to authorisation are completed by other regulations.

Beyond the **general patent rules** applicable to medicines, the **Regulations on supplementary protection certificates (SPCs)**[253] provide for supplementary intellectual property rights extending patent protection for specific medicines. SPCs aim to offset the loss of patent protection for medicines that occurs due to the compulsory lengthy testing and clinical trials these products require prior to obtaining marketing authorisation.

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[250] Proposal for a Regulation of the European Parliament and of the Council on the European Health Data Space, COM(2022) 197 final, Proposal for a regulation - The European Health Data Space (europa.eu).

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

[252] Council Regulation (EU) 2021/2085 of 19 November 2021 establishing the Joint Undertakings under Horizon Europe and repealing Regulations (EC) No 219/2007, (EU) No 557/2014, (EU) No 558/2014, (EU) No 559/2014, (EU) No 560/2014, (EU) No 561/2014 and (EU) No 642/2014, OJ L 427, 30.11.2021, p. 17, EUR-Lex - 32021R2085 - EN - EUR-Lex (europa.eu)

[253] Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the supplementary protection certificate for medicinal products, OJ L 152, 16.6.2009, p. 1, EUR-Lex - 32009R0469 - EN - EUR-Lex (europa.eu) and Regulation (EU) 2019/933 of the European Parliament and of the Council of 20 May 2019 amending Regulation (EC) No 469/2009 concerning the supplementary protection certificate for medicinal products, OJ L 153, 11.6.2019, p. 1, EUR-Lex - 32019R0933 - EN - EUR-Lex (europa.eu).

Table 41 - Overview of the current IP and regulatory protection incentives for medicines

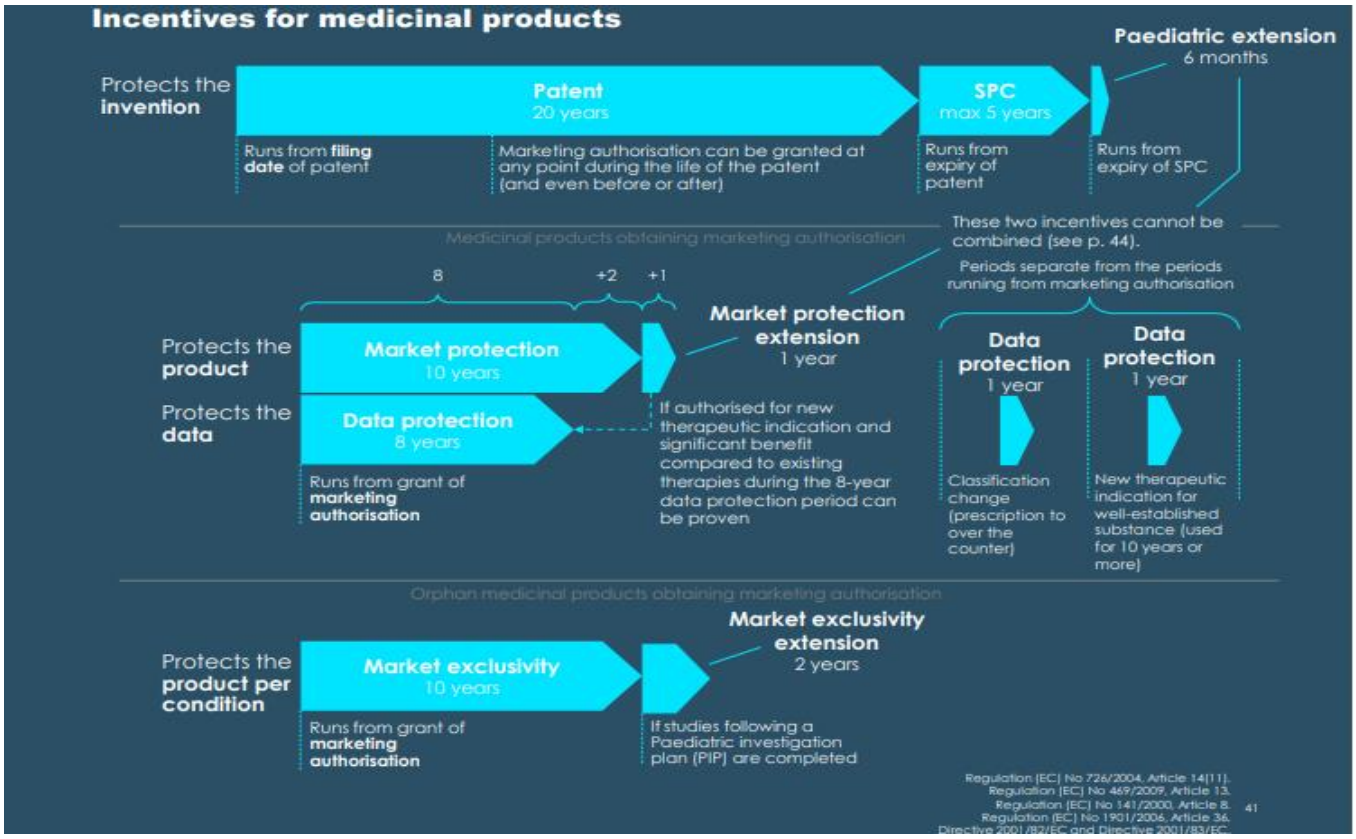

Table 41 above provides an overview[254] of the current IP and regulatory protection rules for medicines in the EU.

The ongoing review of the SPC regulation[255] will put in place a unitary SPC and/or a single ('unified') procedure for granting national SPCs. This will make SPCs more accessible and efficient, and will impact the health sector.

iii. At the market launch stage

Following marketing authorisation companies take decisions on the market launch in Member States based on commercial considerations[256]. These decisions are influenced by the

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

[255] Medicinal & plant protection products – single procedure for the granting of SPCs (europa.eu).

[256] The authorisation of a medicinal product does not mean that it will be immediately accessible to all European patients. Factors such as the size of the population or the organisation of health systems and national procedures influence these decisions. Companies tend to begin negotiations with the Member States that may grant a higher

national decisions on pricing and reimbursement of the medicines concerned, since pricing and reimbursement is the competence of Members States[257].

The **Directive on transparency of measures regulating the prices of medicines** and their inclusion in the scope of national health insurance systems[258] aims at obtaining an overall view of national pricing arrangements, and providing public access to them for all those involved. This Directive regulates the procedural aspects of the Member States' decisions on pricing and reimbursement, e.g. timelines for decisions on pricing and reimbursement, publication of criteria for reimbursement and negative reimbursement decisions have to be justified. It does not impact on the level of price.

To help national authorities in their reimbursement decisions national Health Technology Assessment (HTA) bodies may assess the medicines. The HTA is a scientific evidence-based process to determine the relative effectiveness of new or existing health technologies.

The **Regulation on HTA**[259] establishes a Coordination Group of HTA national or regional authorities, a stakeholder network and lays down rules on the involvement in joint clinical assessments and joint scientific consultations of patients, clinical experts and other relevant experts. The regulation also reduces duplication of efforts for national HTA bodies and industry, facilitates business predictability and ensures the long-term sustainability of EU HTA cooperation. The new rules will come in to force in 2025 and should complement the efforts of the EU general pharmaceutical legislation to incentivise innovation with a strengthened and expanded HTA capacity.

iv. After the market launch stage

Once a medicine is authorised and placed on the market, it is subject to pharmacovigilance. Pharmacovigilance relates to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem. The general EU pharmaceutical legislation details the pharmacovigilance obligations.

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price, often the countries with the highest GDP per capita. The willingness to pay a high(er) price in a Member State with a high GDP may limit the ability of a smaller Member State to negotiate a price in line with its GDP; hence, differences in the accessibility and affordability across the EU.

[257] The decision for pricing and reimbursement is based on national policies, which pertain to Member States and thus are outside the remit of the EU legislation and of this revision.

[258] Council Directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of national health insurance systems, OJ L 40, 11.2.1989, p. 8, EUR-Lex - 31989L0105 - EN - EUR-Lex (europa.eu).

[259] Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU, OJ L 458, 22.12.2021, p. 1, EUR-Lex - 32021R2282 - EN - EUR-Lex (europa.eu).

In addition, the **Regulation on the performance of pharmacovigilance activities**[260] outlines the practical details to be respected by marketing authorisation holders, national competent authorities and the EMA and the **Regulation on post-authorisation efficacy studies**[261] specifies the situations in which such studies may be required.

After an initial authorisation has been granted, market authorisation holders can also develop changes to the medicines. The **Regulation on variations**[262] sets the procedures for post-authorisation changes to a marketing authorisation for medicines. These changes can e.g. be changes in address of the company, active substance, strength, pharmaceutical form or route of administration. The Commission also intends to review this regulation so as simplify the system and reduce administrative burden for medicine authorities and companies.

c. Legislation in adjacent areas

The **legal framework for blood, tissues and cells**[263] (BTC) is used for medical treatments and therapies, including innovative therapies. The ongoing review will promote the safety of patients and donors, facilitate innovation and contribute to adequate supply of the relevant therapies. Blood, tissues and cells may be starting materials for medicines. Particularly important for the pharmaceutical sector is the strengthening the safety and quality requirements of BTC to align with the standards of the pharmaceutical framework for the highest risk preparations. It will also address the (re)emergence of communicable diseases, including lessons learnt from the COVID-19 pandemic, and is thus contributing to the European Health Union.

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[260] Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council, OJ L 159, 20.6.2012, p. 5, EUR-Lex - 32012R0520 - EN - EUR-Lex (europa.eu).

[261] Commission Delegated Regulation (EU) No 357/2014 of 3 February 2014 supplementing Directive 2001/83/EC of the European Parliament and of the Council and Regulation (EC) No 726/2004 of the European Parliament and of the Council as regards situations in which post-authorisation efficacy studies may be required, OJ L 107, 10.4.2014, p. 1–4, EUR-Lex - 32012R0520 - EN - EUR-Lex (europa.eu).

[262] Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products, OJ L 334, 12.12.2008, p. 7, EUR-Lex - 32008R1234 - EN - EUR-Lex (europa.eu).

[263] Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC, OJ L 33, 8.2.2003, p. 30, EUR-Lex - 32002L0098 - EN - EUR-Lex (europa.eu) and Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, OJ L 102, 7.4.2004, p. 48, EUR-Lex - 32004L0023 - EN - EUR-Lex (europa.eu).

The **regulation on medical devices**[264] and **the regulation on in vitro diagnostic medical devices**[265] deal with medical devices, which are products or equipment intended for a medical purpose. In the EU, they must undergo a conformity assessment to demonstrate they meet legal requirements to ensure they are safe and perform as intended. They are assessed at Member State level, but EMA is involved in the assessment sometimes. In some cases, the bodies responsible for the conformity assessment must seek a scientific opinion from EMA before issuing a CE certificate. This is the case essentially when medicines are concerned (e.g. medical devices with an ancillary medicinal substance, companion diagnostics). In some other cases (when the device in ancillary to the medicines), the combined product requires a marketing authorisation.

[264] Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC, OJ L 117, 5.5.2017, p. 1, EUR-Lex - 02017R0745-20200424 - EN - EUR-Lex (europa.eu).

[265] Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU, OJ L 117, 5.5.2017, p. 176, EUR-Lex - 02017R0746-20170505 - EN - EUR-Lex (europa.eu).

ANNEX 8: INTERNATIONAL CONTEXT

Table 42 - **Comparison of criteria for orphan designation in the EU, US and Japan**

	EU	US	Japan
Orphan condition	< 5 in 10,000 in EEA; OR without incentives it is unlikely that the marketing would generate sufficient return to justify the investment.	≤ 6 in 10,000 in US; OR an orphan subset of a non-rare disease; condition where the characteristics of the medicinal product limit its use in a particular subgroup; OR	< 4 in 10,000 in Japan;
Medical need	No satisfactory methods of treatment (or prevention or diagnosis) for life-threatening or chronically debilitating condition exist; OR if any such methods exist the medicinal product must be of significant benefit to those affected by the condition, i.e.: o conferring a clinically relevant advantage; OR o a major contribution to patient care.	Not a criterion unless the same drug has previously been approved for the same use or indication, clinical superiority needs to be proven as follows: Shown to provide a significant therapeutic advantage over an approved drug in one or more of the following ways: (i) Greater effectiveness; (ii) Greater safety in a substantial portion of the target populations; (iii) In unusual cases, where neither greater safety nor greater effectiveness has been shown, a demonstration that the drug otherwise makes a major contribution to patient care.	No appropriate alternative drug/medical device treatment for serious disease including difficult to treat the disease; OR higher efficacy or safety is expected compared with existing products.
Medical plausibility/ scientific rationale	Usually *in vivo* data.	Clinical study data or case reports if available; *in vivo* animal data; *in vitro* data if no clinical or *in vivo* data available	Non-clinical and clinical data in the latter half of the phase I study or in the first half of the phase II study.

TABLE 43 - KEY DIFFERENCES IN THE PROCEDURES FOR ORPHAN DESIGNATION IN THE EU, US AND JAPAN[266]

Items	EU	US	Japan
Application to	Committee for Orphan Medicinal Products (COMP).	Office of Orphan Products Development (OOPD).	Ministry of Health, Labour and Welfare (MHLW)
Timetable	Timetable for submission and assessment published by the Agency.	Any time; no defined timetable;	Any time; no defined timetable;
Key aspects of the application	Prevalence; Medical need; Medical plausibility.	Prevalence. Scientific rationale.	Prevalence; Medical need; Possibility of development.
Sponsor established in territory	Proof of establishment in EU.	Not required.	Not required.
Translations	Translations of product name and proposed orphan indication into all official languages of the EU plus Icelandic and Norwegian.	Not required.	Application in Japanese.

[266] In the US, a medicinal product is eligible for orphan designation when it is intended to treat a disease that affects less than 200 000 persons (which is equivalent to 6 in 10,000) in the US or affects more than 200 000 persons and for which there is no reasonable expectation that the cost of developing and making a medicinal product for such disease or condition will be recovered from sales. In addition, in the US an orphan designation may be given to an orphan subset of a non-rare disease condition where the characteristics of the medicinal product limit its use in a particular subgroup. O'Connor DJ; Expert Opinion on Orphan Drugs (2013), 1(4):255-259.

ANNEX 9: CRITERIA TO IDENTIFY PRODUCTS ADDRESSING UMN AND HUMN

	High UMN **Orphan** medicinal products	UMN **general** pharmaceutical legislation[267]
CRITERIA		
Disease level	Life-threatening or seriously debilitating	Life threatening or seriously debilitating
Product level	[Criteria for designation continue to apply - Article 3 of the Orphan Regulation: <5 in 10 thousand persons in the Community] <u>Case 1</u> • **No medicine is authorised** for the treatment of the disease/condition; **And** • There is **no commonly used (non-pharmacological) method** of treatment whether subject to marketing authorisation or not (e.g. surgery). **And** • The treatment concerns the substantial part of population affected by the orphan disease; **And** • The product does not concern a well-established use product. **[OR]** <u>Case 2</u> • **Treatments exist** but they: - Are symptomatic, not curative; **And** • The treatment under development is a **curative** treatment for the majority of patients affected by the orphan disease.	<u>Case 1</u> • **No medicine is authorised** for the treatment of the disease/condition; **<u>[OR]</u>** <u>Case 2</u> • Medicines are authorised but are not **satisfactory** o Remaining high morbidity or mortality, [or] o Serve less than a certain % of the population affected by the disease, [or] o There is no paediatric indication. **And** <u>In both cases (1 and 2), the new product must:</u> - Have a large treatment effect (reducing morbidity or mortality); [**and**] - Serve a substantial part of population; **[OR]** <u>Case 3</u> - It concerns an **orphan designated medicinal product** that automatically fulfils UMN for general pharma (meaning there is no additional requirement(s))

[267] Criteria applicable also for medicines for children

ANNEX 10: FACTORS INFLUENCING ACCESS TO AFFORDABLE MEDICINES

This annex sets out the different regulatory steps and related decision making processes that have an impact on access and affordability of medicines ("access chain"). Section 1 describes the different steps in the "access chain" from authorisation of medicines to patient access. Section 2 provides further details on pricing and reimbursement policies across the EU and how they can influence access to affordable medicines.

1. **The access chain: from market authorisation of medicines to patient access**

Marketing authorisation is but the first of a number of steps for patients to have access to a medicine. Patient access also requires, following relevant applications by companies, positive HTA assessments and positive pricing and reimbursement decisions by Member States. In addition to those steps, for patients to have access *across the entire EU*, companies have to launch the respective medicine in each Member State. Finally, for a patient to have actual access to a medicinal product, a prescriber has to decide that a medicine is the right treatment choice and prescribe it. The steps from marketing authorisation to patient access can be described along an access chain, which is summarised in the table below. Further details on each step are provided in the following subsections of this section.

Table 44 - Overview *of the access chain: marketing authorisation to patient access*

STEPS	**Scope**	**Legal framework**
1. Marketing authorisation	Quality, safety, efficacy; Positive benefit-risk balance	General pharma framework
2. EU-level Health Technology Assessment (clinical HTA aspects)	Relative clinical effectiveness and relative safety, in comparison to comparator treatment(s) reflecting the standard of care; Supports conclusions on added therapeutic (clinical) value	Regulation (EU) 2021/2282
3. Company decision to launch the medicine in a Member State	Submission of application by the company to national HTA, pricing and reimbursement bodies	

4. National Health Technology Assessment	Takes into account the EU-level assessment of clinical HTA aspects; Focuses on context-specific, non-clinical HTA aspects (e.g. economic, organisational); Supports conclusions on cost-effectiveness, budget impact, value for money	National/regional legislation
5. National pricing and reimbursement	Decisions on reimbursement and pricing; Takes into account added therapeutic (clinical) value, economic considerations (cost-effectiveness, budget impact, affordability), healthcare system and societal context	National/regional legislation Directive 89/105/EEC (covering only timeline, process)
6. Prescription	Evidence-based medicine, taking into account clinical guidelines and medical protocols and the individual patient situation	

1.1 Marketing authorisation

For the marketing authorisation of a medicine, the regulator will consider the quality, safety and efficacy of the medicine and authorise it if the medicine has a positive benefit-risk balance for the patient. Accordingly, data requirements for marketing authorisation reflect the need to show quality, safety and efficacy of a particular medicine. "Downstream" steps in the access chain (health technology assessment, pricing and reimbursement) often require additional data to show an added value of a newly authorised medicine compared to already existing medicines/treatments (see sections 1.2, 1.4 and 1.5).

It should however be noted though that even medicines which appear similar at the time of launch may over time prove to have different efficacy or safety profiles in particular subgroups of patients. Furthermore, the effect of treatment in individual patients may differ from the population-level effects seen in clinical trials. With greater choice, patients will have a better chance of finding a treatment most appropriate to their needs. For these reasons, EU regulations on marketing authorisation do not require that new medicines be superior to medicines already on the market.

1.2 EU-level Health Technology Assessment (clinical HTA aspects)

Health technology assessment (HTA) evaluates the added value of a new medicine in comparison to existing medicines (or other treatments) that reflect the current standard of care. HTA is an evidence-based approach that helps Member States to provide the optimal health care outcome for patients with limited budgets. Accordingly, HTA is used by Member States across the EU in particular for innovative and costly medicines, as a tool to support pricing and reimbursement decisions. However, there is considerable diversity across Member State HTA systems in terms of procedural frameworks, methodological approaches, and available resources and expertise.

In 2022, Regulation (EU) 2021/2282 on health technology assessment entered into force. It provides a legal framework for strengthened EU cooperation on HTA, focusing on clinical aspects of HTA (including the development of common methodologies). From 2025 onwards, Member State HTA bodies will jointly assess *clinical* HTA aspects (comparative clinical effectiveness and safety) of centrally authorised innovative medicines (Joint Clinical Assessment).[268] Such Joint Clinical Assessments will have to be taken into account by Member States in their national HTA processes. Joint Clinical Assessments will be high quality, timely scientific reports (available within 30 days from marketing authorisation). They will enable Member States to focus their limited national HTA resources on assessing more context-specific, non-clinical aspects of HTA (see section 1.4).

Clinical data generated for marketing authorisation purposes (to demonstrate safety and efficacy of the individual product) are not always considered sufficient for HTA and down-stream pricing and reimbursement purposes, which rely on demonstration of comparative effectiveness and safety (i.e. added therapeutic value over existing medicines/treatments).[269,270,271] HTA bodies generally require clinical trials that include an active comparator arm (rather than a placebo-controlled trial or a single-arm trial). HTA bodies also often see challenges with clinical trial data that are less mature and come with higher uncertainties, e.g. in the context of conditional marketing authorisations.[272] When HTA bodies consider the available clinical data inappropriate or insufficient for demonstrating an added therapeutic value, this can lead to delays and

[268] Step-wise implementation of the product scope: oncology and advanced therapy medicines from 2025, orphan medicines from 2028, all centrally authorised innovative medicines (new active substances) from 2030.

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

[270] Bloem LT, Mantel-Teeuwisse AK, Leufkens HGM, De Bruin ML, Klungel OH, Hoekman J. Postauthorization Changes to Specific Obligations of Conditionally Authorized Medicines in the European Union: A Retrospective Cohort Study. Clin Pharmacol Ther. 2019;105(2):426-35.

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

[272] In the interest of public health, a conditional marketing authorisation may be granted for such medicines on less comprehensive clinical data than normally required subject to legally binding obligations for the marketing authorisation holder to generate the comprehensive data after the authorisation.

negative results in the downstream decision-making process on pricing and reimbursement.[273, 270, 271]

From a company perspective, the conduct of clinical trials that generate the comparative evidence required for HTA purposes can be more risky, more costly or take longer. Companies have also faced challenges related to lack of clarity on data needs for HTA, given the diversity of HTA systems and methodological frameworks across Member States. Companies have therefore traditionally (first) focused on the data needs for marketing authorisation when designing their clinical trials. This is however changing and there have been increasing calls by pharmaceutical companies and other stakeholders for more early dialogues on evidence needs along the lifecycle of products and for scientific advice on evidence generation.[270, 271]

For this reason, the new HTA Regulation (Regulation (EU) 2021/2282) provides also a legal framework for scientific advice by HTA bodies to companies on clinical trial design (common HTA advice, agreed at the level of the Member State Coordination Group on HTA), in parallel with scientific advice by the European Medicines Agency provided for marketing authorisation purposes. While respecting the different remits of marketing authorisation and HTA, this parallel scientific advice aims to ensure the generation of evidence that meets the requirements of both frameworks. Parallel scientific advice has already been successfully piloted in the context of EU-funded projects (in particular the Joint Actions EUnetHTA in cooperation with EMA).[274]

1.3 Company decision to launch the medicine in a Member State

It should be noted that while a marketing authorisation at EU level allows for a medicine to be placed on the market in all Member States, the actual market launch in a given Member State is exclusively the decision of the marketing authorisation holder. Company decisions are commercial decisions that take into account whether there is a 'market' for the medicine in a given Member State from a business point of view, considering factors such as market size, price levels, promotion and distribution networks, regulatory requirements, current or future patient population, medical protocols and national pricing and reimbursement policies such as external reference pricing (see Section 2 on pricing and reimbursement policies for further details). Factors related to the healthcare system can also influence the decision, e.g. the availability of specialised equipment or infrastructure to deliver the medicine (in particular in the case of advanced therapy medicines), or national treatment preferences. If the conditions for a positive business case are met, the company will initiate the procedures required for

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[273] Vreman RA, Bouvy JC, Bloem LT, Hövels AM, Mantel-Teeuwisse AK, Leufkens HGM, Goettsch WG. Weighing of Evidence by Health Technology Assessment Bodies: Retrospective Study of Reimbursement Recommendations for Conditionally Approved Drugs. Clin Pharmacol Ther. 2019 Mar;105(3):684-691. doi: 10.1002/cpt.1251. Epub 2018 Nov 8. PMID: 30300938; PMCID: PMC6587700.

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

market launch in that Member State (by submitting applications for HTA, pricing and reimbursement, in accordance with national legal/procedural frameworks).

Smaller and less wealthy countries will often see fewer product entries (due to smaller market potentials). For these countries, the time to availability is also significantly longer. The average time to market from marketing authorisation in Europe differs greatly: for example, for cancer drugs, in the period 2011-2018, it ranged from 17 to 1.187 days, with the shortest delays in Germany, the UK and Austria (less than 31 days) and the longest delays in Greece and Estonia (more than 950 days).[275] In other cases, medicines became available in Central and Eastern Europe only several years after marketing authorisation[276], with market launch delayed up to three years on average in Central-Eastern Europe.[277] It should however be noted that a lack of access to a specific medicine does not necessarily imply lack of access to effective treatment, if appropriate therapeutic alternatives are accessible.[278]

1.4 National Health Technology Assessment

For medicines for which HTA is conducted to support pricing and reimbursement decisions (usually for innovative, costly medicines), the national HTA procedure is usually triggered by marketing authorisation holders launching a pricing and reimbursement application in the Member State concerned.

Currently, HTA bodies assess both clinical aspects (comparative effectiveness and safety) and non-clinical aspects (e.g. economic, organisational, social, ethical) at national level. From 2025 onwards, assessments of clinical HTA aspects will be conducted jointly at EU level (Regulation (EU) 2021/2282), and HTA work at national level is expected to focus on non-clinical HTA aspects (see section 1.2). Clinical HTA analyses support pricing and reimbursement authorities in drawing conclusions on added therapeutic value, while economic HTA analyses support them in concluding on cost-effectiveness, value for money and budget impact.

1.5 National pricing and reimbursement decision

Pricing and reimbursement rules and policies are an exclusive competence of Member States (Article 168 TFEU). Due to historical, political, legal and economic developments, a large variety in pricing and reimbursement regulations have developed across Member States. Moreover, the overall organisation and funding of national healthcare systems differ significantly.279

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[275] Uyl-de Groot, C., Heine, R., Krol, M., and Verweij, J. 'Unequal Access to Newly Registered Cancer Drugs Leads to Potential Loss of Life-Years in Europe, Cancers, 2020.

[276] Vogler, S., Schneider, P., and Zimmermann, N., 'Evolution of Average European Medicine Prices: Implications for the Methodology of External Price Referencing', PharmacoEconomics, 303-309, 2019.

[277] Maini, L., & Pammolli, F., Reference Pricing as a Deterrent to Entry: Evidence from the European Pharmaceutical Market, 2017.

[278] OECD (2018), Pharmaceutical Innovation and Access to Medicines, OECD Health Policy Studies, OECD Publishing, Paris, https://doi.org/10.1787/9789264307391-en.

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

National and/or regional pricing and reimbursement policies assess the size of the patient population and budget impacts, and negotiate the price. Often, late market entries in some Member States are driven by a combination of business decisions and national pricing/reimbursement policies, such as external reference pricing, leading marketing authorisation holders to market their medicines first in Member States where a high price can be obtained (see section 2 on pricing and reimbursement policies across the EU for further details). Some Member States, e.g. Greece, require proof of a positive reimbursement decision in comparable countries before an HTA assessment can be initiated.280

Pharmaceutical expenditure is largely subsidised by national health systems in order to ensure the adequate provision of medicines to all citizens. In this context, Member States adopt measures to regulate the prices of medicines and the conditions of their public funding. Such measures influence the prescription and utilisation of medicines in each Member State and also affect the decisions of and possibilities for pharmaceutical companies to sell their products in national markets. Industry stakeholders claim delays in national pricing and reimbursement decisions that would contribute to postponing the market entry of medicines after the granting of a (central) marketing authorisation. However, a factor that can contribute to delays in national pricing and reimbursement decisions is a lack of appropriate evidence on the added therapeutic value of the product, or evidence that suggests only a minor added therapeutic value (see sections 1.2, 1.4 and 2.2).

Directive 89/105/EEC ('Transparency Directive') is the only EU legal instrument in relation to the applicable national rules on pricing and reimbursement of medicines. The Directive is built on the principle of minimum interference in the organisation of national social security systems. It lays down a series of procedural requirements to ensure the transparency of national decisions on pricing and reimbursement, such as a timeline of 180 days (with the possibility of extension or suspension of the timelines), and procedures such as requirements for publishing the outcomes of national decisions. In light of the Treaty rules on free movement of goods (Article 34 TFEU), the Directive has the objective to avoid barriers to trade created by national measures.[281]

It should be noted that the Transparency Directive refers to the transparency of the pricing and reimbursement process, but not the transparency of prices. In general, prices are publicly available only in form of 'list prices'. These list prices are increasingly disconnected from the actual prices paid. Typically and in particular for products with high price and high uncertainty, confidential price discounts[282] or managed entry

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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).

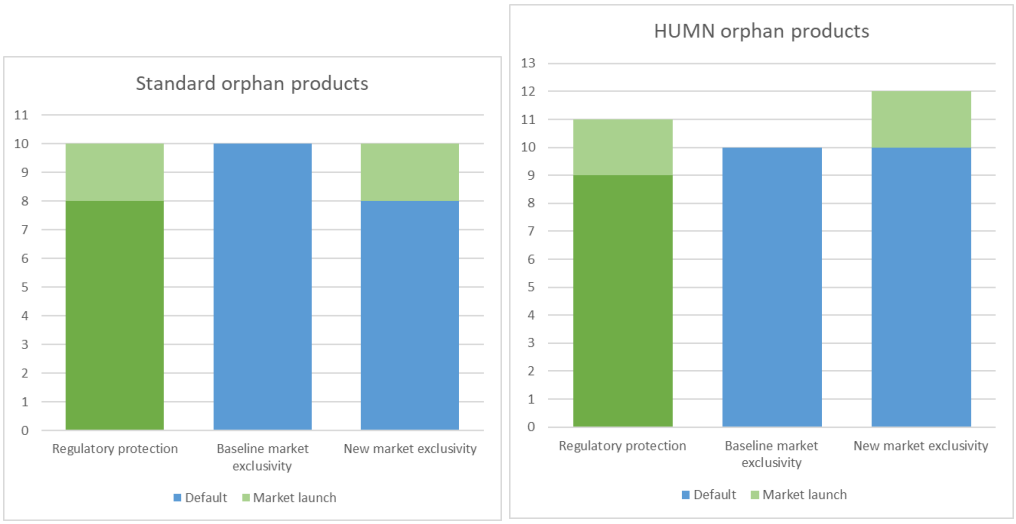
Both the revision of the general pharmaceutical legislation and the revision of the legislation for medicines for rare diseases and children adjust the system of incentives and depart from the 'one size fits all' approach to a 'modulated' one. Therefore, regulatory data protection for medicines and market 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.