EUROPEAN
COMMISSION

Brussels, 11.8.2020
SWD(2020) 163 final

PART 1/6

COMMISSION STAFF WORKING DOCUMENT

EVALUATION

Joint evaluation of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products

{SEC(2020) 291 final} - {SWD(2020) 164 final}

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Glossary

Term or acronym	*Meaning or definition*
Accessibility	A medicine becomes accessible to patients once it has been authorised, is being marketed, and can be reimbursed in a Member State.
Affordability	Relates to payments to be made by patients (out of pocket on healthcare or through co-payments) which can be described as affordability at micro level and to the sustainability of public funding of the healthcare sector raised through social security contributions or taxes (affordability at macro level).
ATMPs	Advanced therapy medicinal products
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 very similar to another biological medicine which has already been approved. Biosimilars are approved if they meet the same standards of pharmaceutical quality, safety and efficacy that apply to all biological medicines.
Cash benefits	Cash benefits are monetary savings associated with reduced hospitalisation and outpatient encounters as a result of reduced avoidable adverse drug reactions.
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.
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.
CMA	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.
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 provides 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.
Extension of marketing authorisation	A change to a marketing authorisation which fundamentally alters its terms. Such changes may have to do with modifications of the active substance, the strength, the pharmaceutical form and/or the route of 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.
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 policy decision-making.
ICER	An incremental cost-effectiveness ratio (ICER) is a summary measure representing the economic value of an intervention, compared with an alternative (the comparator). An ICER is calculated by dividing the difference in total costs (incremental cost) by the difference in the chosen measure of health outcome or effect (incremental effect) to provide a ratio of 'extra cost per extra unit of health effect' for the more expensive therapy versus the alternative.
Impact assessment	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.
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.
Marketing authorisation grant	A decision granting the marketing authorisation issued by the relevant authority.
Market protection	Period of protection during which generics cannot be placed on the market.
Neonatology	A subspeciality of paediatrics consisting of medical care for newborn 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.
Oncology	A branch of medicine that specialises in the prevention, diagnosis and treatment of cancer.
Orphan condition	A medical condition, as defined above, that meets the criteria defined in Article 3 of Regulation (EC) No 141/2000; a life-threatening or chronically debilitating condition affecting no more than five in 10 thousand persons in the EU.
Orphan designation	A status assigned to a medicine intended for use against a rare condition. The medicine must fulfil certain criteria for designation so that it can benefit from incentives such as market exclusivity.
Orphan indication	The proposed therapeutic indication for the purpose of 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 which entered the EU market from the United States before 2000, when there was no special legislation in place.
Payer	An entity responsible for financing or reimbursing healthcare.
PDCO	The Paediatric Committee (PDCO) 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 (PIP) 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 (PUMA) 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 (QALYs) 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.
Repurposed medicines	Existing medicines investigated for new therapeutic indications.
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.
SA	Scientific advice: the provision of advice by the Agency on the appropriate tests and studies required in developing a medicine, or on the quality of a medicine.
SmPC	A summary of product characteristics (SmPC) describes the properties and the officially approved conditions of use of a medicine.
SMEs	Micro, small and medium-sized enterprises
SPC	The supplementary protection certificate (SPC) 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 (SWDs) are required to present the results of all impact assessments and evaluations/fitness checks.

Therapeutic indication	The proposed indication for the marketing authorisation. A medical condition that a medicine is used for. This can include the treatment, prevention and diagnosis of a disease. The therapeutic indication granted at the time of marketing authorisation will be the result of the assessment of quality, safety and efficacy data submitted with the marketing application.
Well-established use	When 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, application for marketing authorisation may be based on results from the scientific literature.

1. INTRODUCTION

The therapeutic landscape for patients in the EU has undergone major changes. Still, considerable unmet needs remain. About 30 million European Union citizens are affected by one of the over 6000 rare diseases currently recognised. The European Union considers diseases to be rare when they affect no more than 5 per 10,000 people in the EU. 80% of these diseases are of genetic origin, and they are often chronic and life-threatening; almost 90% can begin in childhood.

For these patients, and for more than 100 million European children, treatment was either limited or non-existent before the introduction of EU legislation on rare diseases and on medicines for children (in 2000 and 2006 respectively). That situation represented a huge unmet medical need and a significant public health challenge. There were often no medicines at all available for doctors treating patients with rare diseases. Children were regularly prescribed medicines indicated for adults, which had not been tested or adapted specifically for use in young patients. This 'off-label' use of adult medicines comes with the risk of inefficacy and/or adverse reactions in children, who cannot simply be regarded as 'small adults' from the developmental and physiological points of view.

When these policy challenges were identified, the EU already had a well-established legislative framework for medicinal products that had developed considerably since its inception in 1965. It covered the whole life-cycle of medicines, from clinical research to post-marketing surveillance (pharmacovigilance). Its main aim was, and still is, to ensure that all medicines in the Union are authorised by demonstrating their safety, quality and efficacy before they reach patients.

However, this framework was general in nature. It contained no incentives for development in particular areas of medical need. Decisions on product development were generally left to the market and were subject to commercial decisions driven by considerations of return on investment. Public research funding was often the only means available to support neglected fields.

Both the areas of rare diseases and medicines for children were economically unattractive. This was because the market size was generally small and the research and development of products, including the conduct of clinical trials, was more complex. From the 1990s onwards, this led to a policy discussion about how best to correct this market failure and ensure the development of more medicines to treat patients suffering from rare diseases and/or appropriate for use in children. This discussion was influenced by the apparent success of legislative intervention in the US, where orphan and paediatric legislation was introduced in 1983 and 1997 respectively, and was based on the same rationale of imbalance in risk and reward.

In 2000, Regulation (EC) No 141/2000 (hereinafter 'the Orphan Regulation') and in 2006 Regulation (EC) No 1901/2006 (hereinafter 'the Paediatric Regulation') were adopted by the European Commission.

Although the two Regulations are designed to address the same problem, the tools they use differ substantially. The purpose of the Orphan Regulation is to reward research and development through incentives and, ultimately, to place medicines for rare diseases on the market, where there was previously no commercial interest. The Paediatric Regulation, however, works mainly with obligations. It compels companies already developing products for adults to screen them for possible use in children, and only provides rewards once this obligation has been fulfilled, to compensate for the additional costs incurred. [1]

Purpose and scope of the evaluation

The two Regulations are subject to the ex-post evaluation presented in this document.[2] The purpose of the evaluation is twofold. Firstly, it assesses the strengths and weaknesses of the two legal instruments, both separately and in combination with each other. It focuses on how they have catered for products for unmet medical needs, taking into account how pharmaceuticals are developed, science advances, and business models change. Secondly, it provides insights into how the various incentives and rewards for which the Regulations provide have been used, along with an analysis of the related financial consequences, both in general and by stakeholder group.

There are several reasons why the two Regulations are evaluated together. Firstly, they are both designed to tackle a market failure that results in a lack of medicines for the two groups of patients concerned. Secondly, they often address the same therapeutic areas, as the great majority of orphan diseases affect children[3] and many paediatric diseases can be classified as rare. Thirdly, there are some conceptual overlaps, for instance as regards incentives provided to companies where market exclusivity for orphan medicines is extended through the Paediatric Regulation. For these reasons, the Commission Report on the Paediatric Regulation[4] published in 2017 concluded that the two Regulations would need to be assessed together before any amendments could be made.

However, undertaking a joint evaluation has its limitations. For example, as noted above, the two Regulations employ different tools to try to achieve their goals,, making it difficult to analyse and compare the results together. The evaluation also relies on two different studies and on different consultation activities.

The evaluation covers 2000-2017 (Orphan Regulation) and 2007-2017 (Paediatric Regulation) and is based on sound evidence about how the two instruments operate from both a public health and a socioeconomic perspective. It covers five evaluation criteria: the effectiveness, efficiency, relevance, coherence and EU added value of the Regulations.

The evaluation describes the impact of external factors on the Regulations' expected outputs. Those factors include scientific and technological advances, developments in

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1 The Orphan Regulation incentivises new developments while the Paediatric Regulation rewards the companies for testing the possible use of their medicines in children.

2 Ex-post evaluations are used throughout the European Commission to assess whether a specific intervention was justified and whether it worked (or is working) as expected in achieving its objectives and why.

3 Wakap at al, Eur j Hum genetics, (28) p.165, 2019

4 COM(2017) 626.

other jurisdictions, the functioning of national health systems, the commercial strategies employed by companies, and Member States' pricing and reimbursement decisions. Such factors are mostly heterogeneous by their very nature. The EU and its legislation have limited influence on them, and they were not taken fully into account when the legislation was designed. Nonetheless, they affect its performance and relevance. The legislative intervention and its outputs therefore need to be viewed and analysed in the context of these influencing factors.

The evaluation has been carried out at a time when issues of access to medicines, their availability and their affordability are very high on the EU political agenda. A roadmap for a new pharmaceutical strategy was published in June 2020.[5] The purpose of this strategy is to improve and expedite patients' access to safe and affordable medicines and to support innovation in the EU pharmaceutical industry. The orphan area is often seen as a micro-environment exemplifying many of the aspects tackled in the pharmaceutical strategy. Orphan medicines make up a growing share of new authorised products and account for an increasing proportion of Member States' spending on pharmaceuticals. In 2018, almost one third[6] of centrally-authorised medicines (excluding generics and biosimilars) were orphan medicines.

At the same time, access to these products varies widely between Member States. In 2016, the Council called on the Commission to examine the impact of pharmaceutical incentives on the availability and accessibility of orphan medicinal products.[7] The European Parliament also debated the issue of access to medicines[8], including medicines for children. In its 2016 Resolution[9], Parliament recognised that the Paediatric Regulation has been beneficial to children overall, but less effective in certain therapeutic areas (e.g. paediatric oncology and neonatology). It therefore called on the Commission to consider revising the Regulation.

The results of this evaluation will guide reflection on any future changes to the legislative framework.

2. BACKGROUND TO THE INTERVENTION

Description of the intervention and its objectives

The last half-century has witnessed significant progress in the field of medicines, benefiting patients and society in general. However, substantial gaps remain in the therapies available. This is especially true both for patients suffering from a rare disease, and for children in general.

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5 https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/12421-Pharmaceutical-Strategy-Timely-patient-access-to-affordable-medicines

6 Data obtained from the Agency.

7 Council conclusions on strengthening the balance in the pharmaceutical systems in the EU and its Member States https://www.consilium.europa.eu/en/press/press-releases/2016/06/17/epsco-conclusions-balance-pharmaceutical-system/

8 'Options for improving access to medicines'; EP resolution of 2 March 2017 (2016/2057(INI)).

9 EP resolution of 15 December 2016 on the regulation on paediatric medicines (2016/2902(RSP)) http://www.europarl.europa.eu/doceo/document/TA-8-2016-12-15_EN.html#sdocta7

Although rare diseases affect a limited number of people per disease, collectively they affect one person in every 17 people within Europe. Obtaining the correct diagnosis is a long and difficult journey in itself. It takes an average of five years to diagnose a child with a rare disease. However, even if a disease has been identified, very few medicines are available, and for many rare diseases there is no pharmaceutical remedy at all. At the time of the EU's intervention via the Orphan Regulation, companies generally had limited interest in developing medicines for rare diseases. They considered it unlikely that the cost of development would be recovered by selling the product to small numbers of patients at the 'normal' prices envisaged.

Similar problems existed with medicines for children. Many products used for children were prescribed and administered on the basis of the doctor's own experience rather than on the results of clinical research. Moreover, medicines were not available in a pharmaceutical form suitable for children. Paediatricians had to use medicines authorised for adults by adapting the dosage, for example by simply crushing adult-size tablets. With some notable exemptions, such as childhood vaccines – one of the success stories of modern medicines – companies were often uninterested in investing in paediatric medicines. This often meant conducting research and development for a small number of patients, given that children are not a uniform sub-group of patients; different growth and maturation rates require multi-national trials. Furthermore, as recently as the 1980s, paediatric clinical trials were stigmatised, it being thought that children should be protected from participating in medical research.

At the end of the 1990s, the pharmaceutical market was dominated by big companies, which were often interested in developing 'blockbusters' that could be sold in large volumes to tackle common diseases. By contrast, the costs of research and development meant that industry was often disinclined to invest in developing remedies for diseases with small numbers of patients.

The 'standard' incentives provided by the general legislative framework for pharmaceuticals (8 years of data protection, 10 years of market protection and 20 years of patent protection) were failing in these areas. They were not considered enticing enough. In other words, they did not ensure a large enough return on investment to make it worthwhile for companies to develop orphan medicines or to research medicines suitable for paediatric use. It would be wrong to assume that there were no medicines in these areas before the relevant legislation was adopted, as some such products did reach the European market. However, without a specific framework, there was no certainty that such medicines would be developed for and placed on the EU market. The number of medicines available was considered insufficient, both in absolute terms and in comparison with other regions.

Member States tried to boost the development and commercialisation of orphan and paediatric medicines through various national measures, which were not coordinated, and by funding programmes of research into rare diseases. However, these activities had almost no success and raised concerns that such scattered attempts could lead to distortions of the EU internal market.

Other regions were more successful. Starting in the 1980s, the US and Japan introduced specific legislative frameworks to foster the development of medicines to treat rare diseases or for use in children.

The explanatory memorandum[10] of the orphan legislative proposal prominently refers to the success of US legislation, where, over 13 years (1983-1996), 837 products were awarded the status of orphan drug, 323 were aided by grant programmes, and 152 obtained marketing approval. Unsurprisingly, therefore, EU orphan legislation shares parts of its design with the US model. The prospect of obtaining market exclusivity for a given period, during which companies would recover their investment, seemed at the time to be the best way of copying the success of the US system.[11] It was also recognised that market exclusivity would not be the only major incentive. It would be up to the Community and the Member States, within their respective spheres of competence, to provide other incentives for developing medicines for rare diseases. It was thought that the Community would support research, while Member States would provide tax incentives.[12]

As regards remedies for common diseases, it is quite usual for products developed in another region to find their way to Europe eventually. However, the increase in orphan and paediatric products in the US did not automatically lead to a similar increase in the EU. Only some such products were placed on the EU market at the same time.

For orphan medicinal products, this might have been due to the administrative and logistic costs (authorisation fees, costs of legal representatives and staff responsible for conducting batch releases, maintenance costs) associated with a marketing authorisation for low-volume products. Another possible reason was the lack of specific measures to protect such products from generic competitors in the EU. These factors meant that the business case for placing such products on the market was not particularly strong. In a survey conducted for this evaluation, respondents referred to a combination of scientific, financial and regulatory hurdles as the biggest entry barriers facing developers.[13]

As regards medicines for children, even where companies had collected data on their use in children to obtain a marketing authorisation in the US, they had nothing specific to gain by providing such data to the EU on their own initiative. In many cases, the increase in sales volume of adult medicines achieved by extending use to children was not very sizeable, and it had to be balanced against the additional costs of maintaining more complex marketing authorisations serving different populations.

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10 Introduction of the explanatory memorandum to the Commission proposal for the Orphan Regulation (COM(1998) 450 final).

11 Alternatively, the EU would have needed to rely on 'free-riding' of US-approved medicines, which could have had a negative impact both on the number of orphan products and their timely availability to EU patients. Moreover, some Member States had considered acting independently at the time, and therefore EU action was considered necessary to avoid distortion of the internal market in an already heavily regulated field of medicines.

12 Section 'Other incentives' in explanatory memorandum (COM(1998) 450 final).

13 Section 6.1.1 of the 2019 Orphan study report.

The objectives and main design features of the two regulations

Orphan Regulation

The specific objectives of the Orphan Regulation are to:

- Ensure research and development and the placing on the market of designated orphan medicinal products (***availability***) (specific objectives 1 and 2);
- Ensure that patients suffering from rare conditions have the same quality of treatment as any other patient (***accessibility***) (specific objective 3).

Products fall under the scope of the Orphan Regulation if they either fulfil the '*prevalence criterion'* of no more than 5 in 10,000 people affected by the disease in the EEA or the '*insufficient return upon investment criterion*', meaning that, without incentives, it is unlikely that the marketing of the medicinal product in the EU would generate sufficient return to justify the necessary investment. Furthermore, the condition in question has to be life-threatening or chronically debilitating. No satisfactory treatment should exist in the EU, or, if it exists, the product in question should provide a significant benefit[14] to patients affected by that condition in comparison with the existing treatment.[15]

The Regulation establishes a **two-step EU procedure**:

- First, a company may request that a product be granted an '**orphan designation**' by the European Commission, based on a positive opinion adopted by the European Medicines Agency (hereinafter 'the Agency') at any stage of development. An early orphan designation may allow developers (researchers, SMEs or big pharma companies) to secure R&D financing, either through the EU research framework or through a national funding mechanism, and may help attract investors more easily.[16] In addition, an orphan designation may enable a product to receive dedicated support from the Agency, such as scientific advice (known as protocol assistance for orphan medicines)[17], before the Agency grants marketing authorisation.
- Once the development is completed, the product can, as a second step, benefit from an **EU-wide marketing authorisation**.[18] If, at the time of granting the marketing authorisation, continued compliance with the designation criteria is confirmed, the product will enjoy a **monopoly period of 10 years** ('market exclusivity')[19], which can be extended to 12 years if a paediatric research and development programme is completed (see Figure X).[20] If the designation is not confirmed, the company will receive a standard marketing authorisation. (It is noteworthy that US legislation does not include a check on continued compliance with the designation criteria at the time of granting a marketing authorisation.) Once the Agency has granted market exclusivity at the request of a Member State, the monopoly period may be

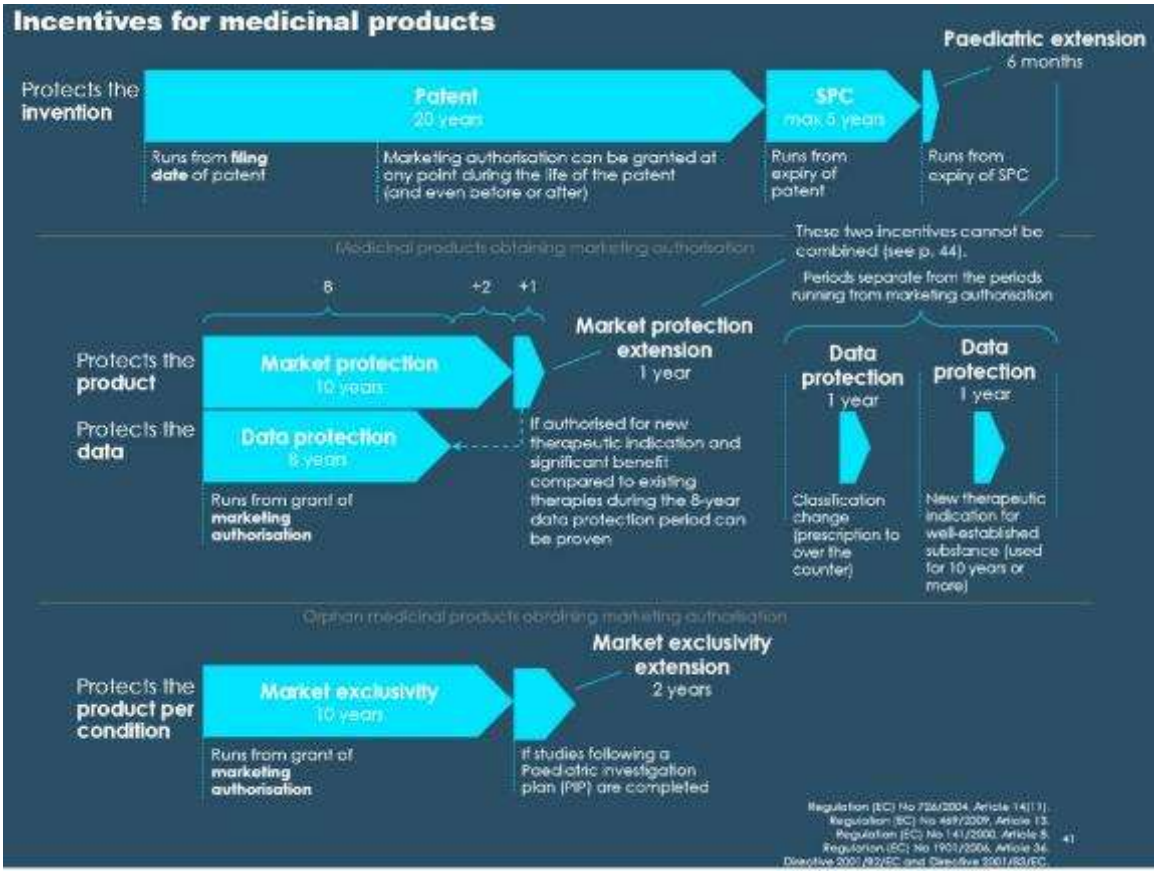
14 See Article 3(2) of (implementing) Regulation No 847/2000.
15 Article 3(1) sub b of the Orphan Regulation.
16 Article 9(1) of the Orphan Regulation.
17 Protocol assistance offers the sponsor of a designated orphan medicine the possibility of requesting advice from the Agency on the conduct of tests and trials, as it is a scientific advice for medicinal products which receives an orphan designation (Article 6 of the EU Orphan Regulation).
18 Regulation 726/2004.
19 See Article 8 of the Orphan Regulation.
20 See Article 37 of the Paediatric Regulation.

shortened to six years if it is established after five years that the product no longer meets the orphan designation criteria.[21]

It was expected that the provisions and the various incentives created by the legislation would help boost research and development and increase the number of orphan medicines available to patients in the EU. It was anticipated that between 5 and 12 applications for orphan designation and for marketing authorisation would be submitted annually between 2000 and 2002.

In the long term, the Regulation would improve the survival rates, life expectancy, therapeutic possibilities and/or the quality of life of patients with rare diseases. Given the generally long development cycles of pharmaceuticals (up to 10-15 years)[22] the legislation was not expected to have an immediate impact. Rather, the intention was to change the therapeutic landscape gradually over time.

Figure 1: Graphic showing the various incentives for developing pharmaceuticals[23]



21 Article 8(2) of the EU Orphan Regulation.

22 Section 1.4.2. of the Study on the economic impact of the supplementary protection certificates, pharmaceutical incentives and rewards in Europe (2018).

23 Chapter 2.1 of the Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe (2018).

Paediatric Regulation

The Paediatric Regulation, designed to tackle the lack of appropriate medicines for children in Europe, has three specific objectives:

- Enable high-quality clinical research in children (specific objective 1);
- Ensure, over time, that most medicines used by children are specifically authorised for such use with age-appropriate forms and formulations and are made available (specific objectives 2 and 3);
- Increase the availability of high-quality information about medicines for use in children (specific objective 4).

To achieve these objectives, the Regulation has established **a system of obligations compensated by rewards**. Companies are obliged to screen every new product they develop for its potential use in children, thereby gradually increasing the number of products with paediatric indications and paediatric information. The possibility of obtaining certain rewards compensates for the burden thus created.

In practice, at an early stage in the development of any new medicinal product, companies have to agree with the Agency on a paediatric research and development programme (a '**paediatric investigation plan'** (PIP))[24], or to obtain, under certain conditions, a derogation (waiver) from this obligation.[25] As a general rule, paediatric clinical studies must be conducted in parallel with adult studies, unless it has been agreed that some or all of the paediatric studies can be deferred**.**[26] Such 'deferrals' are granted if conducting the paediatric studies concurrently would delay the marketing authorisation for adults.

Compliance with the obligation is checked when the company files a marketing authorisation application for the (adult) product. In the event of non-compliance, the application is rejected for use on either children or adults.

If the PIP is completed and all the agreed studies have been conducted, the company may benefit from one of two mutually exclusive rewards:

- **A six-month extension of the** supplementary protection certificate (SPC, an intellectual property right that serves as an extension to a patent) (see Figure 1). The SPC[27] extension[28] covers the entire *product*, not only the *paediatric* part. Extension of the SPC is not automatic; an application must be submitted to the national patent office and filed two years before the SPC expires,[29] or
- **A two-year extension of the orphan market exclusivity** for orphan medicines.

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24 Articles 15 and 16 of the Paediatric Regulation, No 1901/2006.
25 Article 11 of the Paediatric Regulation, No 1901/2006.
26 Articles 20 and 21 of the Paediatric Regulation, No 1901/2006.
27 The SPC system is codified in Regulation (EC) No 469/2009.
28 The SPC adds up to a maximum of five years of additional patent time for innovative active ingredients for medicinal products in cases where they have lost more than five years of effective protection owing to the length of time taken by R&D.
29 Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009.

The reward is granted even if the studies show that the product is unsuitable for paediatric use.

Independently, a specific **paediatric-use marketing authorisation (PUMA)**[30] has been put in place to drive the development of paediatric indications for existing authorised products (no longer covered by a patent or an SPC), by offering the same protection. This is an **8-year period of data protection in parallel with the 10-year market protection period,** as applies to any newly authorised medicinal product. These protections are intended to make investment into existing molecules viable, as new paediatric indications would be protected from immediate competition with generic medicines already present on the market. The PUMA scheme is complemented by EU research funding provided for studies of possible paediatric use of old medicinal products no longer covered by patents or SPCs.

Finally, to make use of existing data to update product information on existing authorised medicines, companies are required to provide the Agency or the national competent authorities with any data they have from completed paediatric studies.

Both Regulations established dedicated committees within the Agency to deal with scientific assessment: the Orphan Committee (COMP) and the Paediatric Committee (PDCO).

It was expected that the obligation to agree on and conduct a PIP for any new product developed would boost clinical research in children. The rewards would compensate for the costs incurred in meeting that obligation. This would result in an increase in the number of medicines with paediatric indications. Moreover, gathering information on clinical studies involving children that have already been conducted or are ongoing, together with greater transparency of paediatric clinical trials, would give doctors a wider view of the treatments available.

The expected impacts were to have scientifically validated therapeutic options and to improve child patients' quality of life. Given the generally long development cycles for pharmaceuticals (10-15 years), the legislation was not expected to have an immediate impact. Rather, it was expected that it would change the therapeutic landscape gradually over time.

Other important factors influencing the field of application of the legislation

Any legislative intervention in a sector such as pharmaceuticals navigates in a complex environment, where external factors influence the performance of legislation. Figure 1 outlines the basic steps in the process of medicine development, showing the long development time from the research discovery to the clinical development of a medicine.

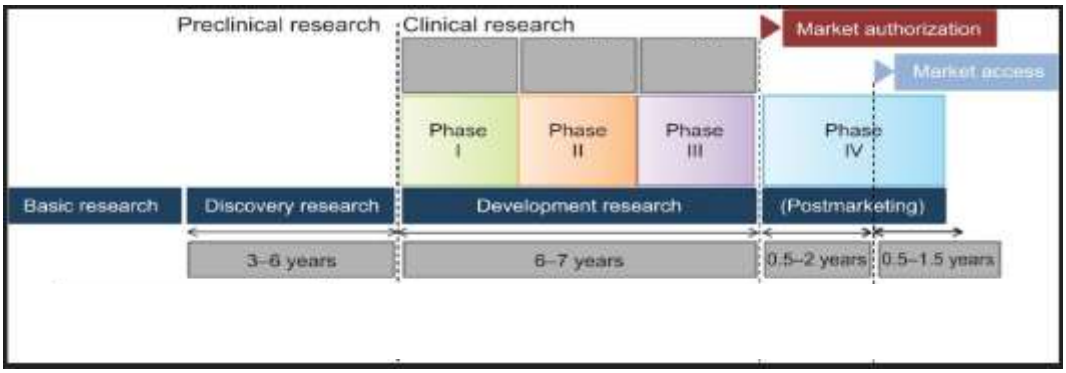
Medicine development is influenced by advances in science. Even the best designed intervention may not succeed if it is not supported by sufficient progress in basic research and solid scientific leads for product development. The complexity of clinical trials for

[30] Article 30 of the Paediatric Regulation.

paediatric and rare diseases also plays a significant role for the development of these products. Legislation may act as enabler, but cannot substitute the inherent research challenges that affect product development.

Considerable support for orphan and paediatric research, both at EU and national levels, including 'national rare disease plans', complement the Regulations. Such support helps pharmaceutical companies to secure R&D financing once the product is designated as orphan. Some Member States have also introduced reduced fees for registration and academic clinical trials, tax reductions or waivers, public funding for research, and free scientific advice. However, neither the Regulations nor research programmes provide for any specific monitoring arrangements to gather data on the relationship between research funding and developments in new orphan or paediatric medicines. This makes it difficult to estimate their impact.

Figure 2: Basic steps in the medicine development process (adapted from scientific literature[31], no specific references to the development timelines of orphans or paediatrics)



The availability, accessibility and affordability of medicines for patients across the EU, including orphan and paediatric medicines, are strongly influenced by factors that go *beyond* the Regulations and/or the remit of the EU.

Pharmaceutical companies' strategic decisions on whether (and where) to launch innovative medicines are often influenced by national pricing and reimbursement considerations falling outside the remit of the pharmaceutical legislation, or by the areas where they focus developments. For example, external reference pricing, used by many countries to determine the price paid for a medicinal product, is one of the reasons why companies often decide to launch their products first in the wealthiest Member States. The size of the population, as well as the organisation of health systems and national administrative procedures, are also reported as factors that influence such decisions.

Another important factor is how medical professionals decide what medicine to prescribe. For example, when a paediatric product is launched, it can take a while before doctors

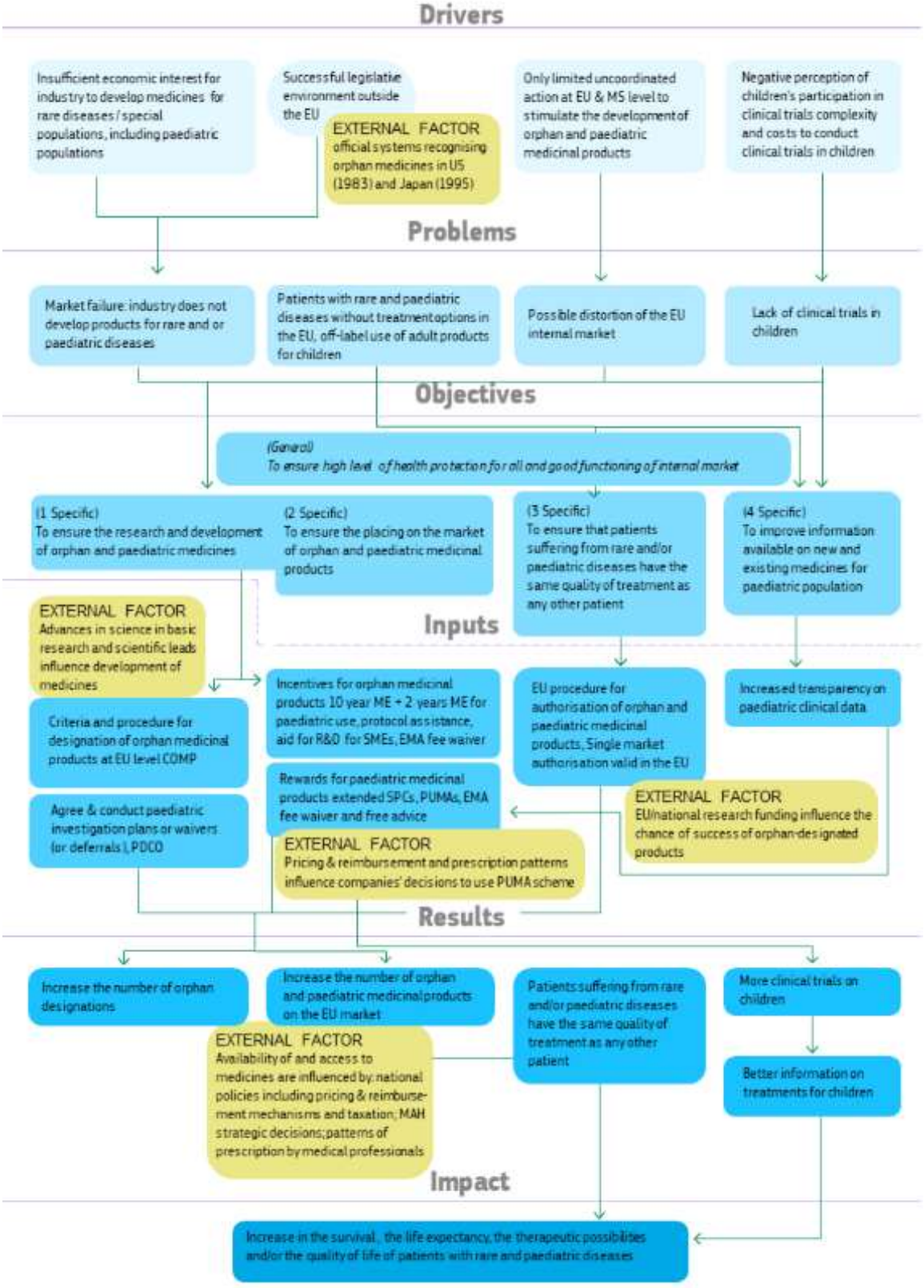
[31] Ciani O, Jommi C. The role of health technology assessment bodies in shaping drug development. DrugDes Devel Ther. 2014;8:2273-2281 https://doi.org/10.2147/DDDT.S49935

switch to prescribing it in preference to a more familiar ‘off-label’ product for adult patients.

These external factors are not new; they existed before the Regulations were adopted. However, they have increased in importance and influence over time, particularly where orphan medicines are concerned.

Chapter 5 analyses the impact of external factors in more detail.

Figure 3: Intervention logic underpinning legislation on orphans and paediatrics



Baseline and points of comparison

The baseline used for this evaluation is the situation in the EU prior to the adoption of the two Regulations.

No impact assessment was carried out for the Orphan Regulation. The baseline has therefore been reconstructed as far as possible on the basis of available data.[32]

To this end, desk research in the context of the orphan study identified the number of products which, by 2000, had been authorised by the Commission for the treatment of a rare disease. 15 medicinal products[33] were authorised at EU level for the treatment of rare diseases of the immune, blood or genito-urinary systems.[34] These products were brought to the market by 12 individual pharmaceutical companies.[35] In addition, 70 medicinal products authorised as orphans in the US were available in at least one Member State. The majority of these 70 products were substances acting on the immune system.[36] [37] These products are referred to throughout this document as 'orphan-likes', indicating that they were not formally labelled as orphan products, but were likely to serve the rare disease population in the EU.

It took up to three years after the US marketing authorisation for the medicines to become available in the first Member State. After three years, they had reached three to four Member States.[38]

However, we should stress that even without any legislative intervention between 2000 and 2017, some additional orphan medicines would have been placed on the market in the EU anyway. Accordingly, not all the products authorised during this period can necessarily be attributed to the legislation. This issue will be dealt with in further detail in Chapter 5.1.

The baseline for *paediatric* medicines is derived from the impact assessment conducted before the adoption of the Paediatrics Regulation, and it is complemented by data from a report provided by the Agency in 2012.[39]

The impact assessment analysed several options: (1) no action; (2) self-regulation by industry; (3) Member State initiatives only; (4) introducing obligations for companies decoupled from rewards and incentives without obligations; (5) data protection or (6) market exclusivity for new paediatric products; (7) market exclusivity for development of

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32 See, for instance, the Interim report on Orphan diseases and drugs (Saphir Europe), February 1995, and Section 2.1 of the Study to support the evaluation of the EU Orphan Regulation (Technopolis Group and Ecorys – August 2019).

33 5 of these 15 products belonged to the group of 'immunomodulating agents', 3 addressed diseases of the blood & blood-forming organs like leukaemia, and another 3 addressed diseases of the alimentary tract and metabolism. The rest addressed diseases of the genito-urinary system and the nervous system.

34 Orphanet Report Series, 2019.

35 See Orphan study report (2019), Section 2.3.

36 See Orphan study report (2019), Section 2.2.

37 Like endocrine therapy, immunostimulants or immunosuppressants.

38 See Orphan study report (2019), Section 2.2.

39 5-year Report to the European Commission, General report on the experience acquired as a result of the application of the Paediatric Regulation.

paediatric developments from 'old' products. It concluded that if no action were taken, the existing situation (absence of medicines tested and authorised for children) would persist. No positive changes had been observed in the EU, even after the introduction of paediatric legislation in the US. And without obligations, the pharmaceutical industry would continue to avoid developing paediatric products.

Depending on the therapeutic area concerned, between 50% and 90% (for example, cancer treatments and HIV treatments) of authorised medicines in the EU were used off-label in children, i.e. without their effects on children having been studied. In addition, information on the outcome of studies conducted on children was not systematically available. It was thus often unclear for doctors treating children whether paediatric use of a particular product was authorised, whether there were insufficient data, or whether existing data showed that the medicine had negative effects when used in children.[40] Looking, for example, at the 317 centrally authorised medicines available at the time, around 78% were relevant to children, but only 34% were authorised with a paediatric indication.[41]

The selected option in the impact assessment combined some of the individual options mentioned above in a manner that would lead to a legislative framework very similar to the one already in place in the US. It was expected that a growing proportion of the available medicines would be tested on children and that the supply of products licensed for use on children would increase. The 'best case scenario' was described as follows:

- After 10-15 years, all patent-protected medicines (unless specifically exempted) would be studied in children, but it could take up to 20 years before the majority of tested products would be authorised for use in children.
- The PUMA system, together with accompanying measures such as EU research funding, would help to foster paediatric research on off-patent products. However, it was recognised that as the associated incentives were weak, the scheme would be unlikely to result in the authorisation of a sizeable number of new products.
- The increased availability of paediatric medicines would change over time with prescription practices. While this would gradually reduce off-label use in children, such use was not expected to disappear completely.
- European R&D would be boosted directly or indirectly, improving the competitiveness of EU companies in comparison with their US competitors. However, it was noted that the way the legislation was framed, and in particular the incentives selected, might push paediatric research towards the most profitable areas, rather than towards providing for patients' unmet needs.
- The testing of medicines in children would cut costs for national health systems, as adverse effects would be reduced, for instance, as would hospitalisations associated with the off-label use of medicines not tested in children. Though this cost reduction could not be quantified, it was thought to be sufficient to offset the costs

40 The Agency's five-year report (Section 3).

41 COM(2004)599 final Commission extended impact assessment and the Agency's five-year report to the Commission (Section 3).

that health systems would incur through the delay in the marketing of generics arising from the reward of SPC extension.

To assess how the legislation has been performing, it may also be helpful to consider the baseline in terms of research funding. Before the introduction of the two Regulations, not only was the pharmaceutical industry not interested, but the research community also showed limited interest.

This meant that for the vast majority of rare diseases, understanding of the natural history of the condition and the underlying causes of a disease was limited or even non-existent. Research funding only started to pick up in the years preceding the adoption of the legislation, but still in relatively small amounts and without coordination.

The fourth EU Framework Programme for Research and Technological Development (1994-1998), for example, sought to improve knowledge of rare diseases through relatively low funding (€7.5 million).[42] At national level, some Member States[43] had adopted specific measures to increase their knowledge of rare diseases and improve detection, diagnosis, prevention or treatment. France, Italy and Spain started to introduce specific national policies to boost the development of orphan medicines. This will be described in more detail in Chapter 5.4.

As regards research on children, the major problem in Europe was the limited number of clinical trials involving children. Some paediatric therapeutic areas, such as neonatology, were particularly neglected. Conducting clinical trials on small populations, such as children affected by a specific disease, would have required multinational trials to be started in most cases, which was complex and costly. One should also bear in mind that it was common as recently as the 1980s to assume that children should be protected from clinical trials. Only later was it recognised that clinical research in children was necessary, but that it should be conducted within a framework which ensured that ethical principles were respected and minors protected from abuse. These aspects were subsequently reflected in the EU Directive on clinical trials, adopted in 2001.[44]

Other points of comparison

In addition to comparing the situations in the EU *before* and *after* the entry into force of the Orphan and Paediatric Regulations, this evaluation refers to other regulatory systems

[42] Allocated to 23 projects for basic research, clinical research, and to set up European registries and databases and pan-EU rare disease networks.

[43] See Orphan study report (2019), Section 2.5 (France, Italy, Spain, Denmark and Sweden).

[44] Directive 2001/20/EC.

(mainly the US for orphan and paediatric medicines and Japan for orphan medicines).[45] A benchmark with the US will complement Chapter 5.[46]

[45] Comparison of availability and access in the EU to medicines that came to the market through orphan jurisdictions in the US and Japan before 2000. See also Section 2.2. of the Orphan study report (2019).

[46] Using data from a US Government Accountability Office Report on orphan drugs (November 2018).

3. IMPLEMENTATION / STATE OF PLAY

Description of the current situation

The development of a new medicine is generally a long process, taking 10 to 15 years.[47] The full effects of legislative intervention are therefore not immediately visible, emerging only gradually.

3.1. Orphan Regulation

The Orphan Regulation has been implemented in full, including the setting up of the Committee for Orphan Medicinal Products (COMP). The provisions of the main act were complemented by additional provisions needed to implement the criteria for designation of a medicinal product as an orphan medicine (definitions of 'similar medicinal product' and 'clinical superiority'). Several guidance documents were adopted, some of which are regularly updated:

- Guidance on Article 3 (criteria for designation), Article 5 (procedure for designation and removal) and Article 7 (Union marketing authorisation - updated in 2016);[48]
- Guidance on Article 8(1) and (3) on the assessment of similarity of medicinal products versus authorised orphan medicines benefiting from market exclusivity;[49]
- Guidance on Article 8(2) for reviewing the period of market exclusivity.[50]

In addition, to reduce the barriers to innovation in medicinal products facing SMEs, Commission Regulation (EC) No 2049/2005[51] determined in 2005 that the Agency should provide scientific advice on designated orphan medicines free of charge to SMEs. Under the Paediatric Regulation, it became possible for orphan paediatric medicines to be granted two additional years of market exclusivity. There have been several court cases concerning the correct interpretation of Articles 3, 5, 7 and 8 of the Orphan Regulation.[52]

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47 Chapter 1 of the Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe (2018).

48 Commission notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products; C/2016/7253; OJ C 424, 18.11.2016, pp. 3–9.

49 Guideline on aspects of the application of Article 8(1) and (3) of Regulation (EC) No 141/2000: Assessing similarity of medicinal products versus authorised orphan medicinal products benefiting from market exclusivity and applying derogations from that market exclusivity.

50 Guideline on the aspects of application of Article 8(2) of Regulation (EC) No 141/2000: Review of the period of market exclusivity of orphan medicinal products.

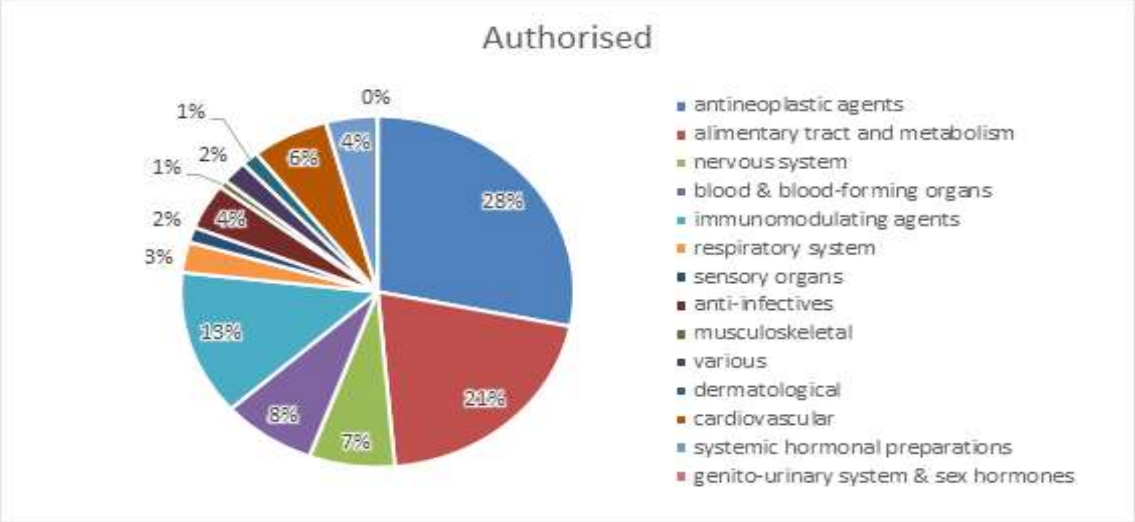
51 Commission Regulation (EC) No 2049/2005 of 15 December 2005 laying down, pursuant to Regulation (EC) No 726/2004 of the European Parliament and of the Council, rules regarding the payment of fees to, and the receipt of administrative assistance from, the European Medicines Agency by micro, small and medium-sized enterprises.

52 Section 3.4 of the Orphan study report (2019).

A Commission staff working document, published in 2006,[53] stated that the EU's orphan legislation had exceeded initial expectations. In the first five years, 22 orphan medicines were authorised for the treatment of 20 different life-threatening or chronically debilitating rare diseases. It was possible that over one million patients suffering from these orphan diseases in the EU had benefited from the availability of these new treatments.

By 2017, 142 unique orphan medicines had *received* an EU marketing authorisation for 107 orphan indications. In a best case scenario, they were estimated to address the needs of 6.3 million EU patients (out of 35 million people suffering from rare diseases in the EU).[54] Of these medicines, 13 were authorised for more than one orphan disease, and a separate period of market exclusivity was granted.[55]

Figure 4: Therapeutic areas covered by authorised orphan medicinal products in 2017



Source: European Commission

Among both designations and authorised products, the largest share (Figure 4) is for anti-cancer treatments, followed by treatments for conditions of the alimentary tract and metabolic disorders. Overall, designations have covered a broad spectrum of therapeutic indications.

For the treatment of acute myeloid leukaemia alone there are 74 designations. Other diseases that have received attention are: glioma (56 designations), cystic fibrosis (51

53 Commission Staff Working Document on the experience acquired with the Orphan Regulation from 2000 to 2005.

54 Section 5.2. of the Orphan study report (2019).

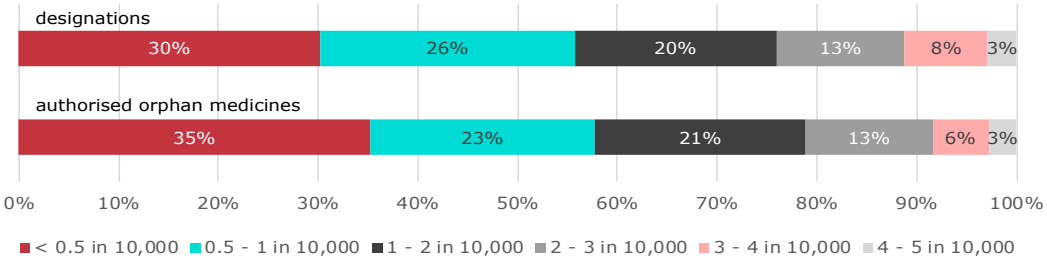
55 These numbers are further benchmarked against the performance of the Orphan Drugs Act in the United States in Chapters 5.1 (effectiveness) and 5.2 (efficiency).

designations), pancreatic cancer (47 designations), ovarian cancer (40 designations), multiple myeloma (32 designations) and Duchenne muscular dystrophy (31 designations).

The US Food and Drug Administration approved 351 orphan drugs for marketing between 2008 and 2017. 53% of these approvals were in one of two therapeutic areas that were also common for granted designations: oncology (42%) and haematology (11%).[56]

The distribution by prevalence is very similar among designated and authorised products (Figure 5). Around a third of products are for treatments with a prevalence of less than 0.5 in 10,000. These are mainly products for the treatment of diseases affecting the musculoskeletal system.

Figure 5: Share of designations and authorised orphan medicines by prevalence



Source: The Agency data, 2018.

Whereas in the past the vast majority of medicines were small chemical molecules, nowadays many new treatments are based on more complex biological products, such as proteins, antibodies or other large molecules, produced by means of biotechnology. They account for around one fifth of all 107 orphan designations.[57] Moreover, the share of advanced therapy medicinal products (ATMP) had shot up to around 18-20% of all new designations by 2016 (with a small decline of 14% in 2017).

Another general market development worth noting is the trend for larger pharmaceutical companies to purchase promising medicines at a late stage of R&D from smaller companies, instead of doing the research (or the basic part of it) themselves.[58]

3.2. Paediatric Regulation

[56] US Government Accountability Office Report on orphan drugs (November 2018), p. 23. See further elaboration of the benchmark with the US in Chapter 5.1 (effectiveness).

[57] Section 5.4.4. of the Orphan study report (2019).

[58] https://www.forbes.com/sites/nicolefisher/2015/04/22/are-ma-replacing-rd-in-pharma/#4f7c8116a21d

All but one of the provisions established by the Paediatric Regulation have been implemented, including the setting up of the Paediatric Committee (PDCO).[59]

The provisions of the main act were complemented by the specific guidance document:

- Guidance on format and content (updated in 2014)[60]

The provision mandating the creation of a distinctive symbol to be placed on products authorised specifically for paediatric indications was not implemented, as it was found that it could have been confusing for parents.[61]

More clinical trials for children

The number of agreed paediatric investigation plans (PIPs) exceeded 1000 in 2018, of which 450 were completed by June 2018.[62] The agreed PIPs covered a wide range of therapeutic areas, with infectious diseases (12%), oncology (10%) and endocrinology/metabolic diseases (9%) at the forefront. However, no particular area was dominant (Table 1).

There has been a clear upward trend in the number of completed PIPs, with over 60% finalised in the last three years. Currently, the conditions with most completed PIPs are immunology/rheumatology (14%), infectious diseases (14%), cardiovascular diseases and vaccines (10% each), with oncology and endocrinology/metabolic diseases accounting for only 7% of the completed PIPs.

In parallel, until 2018, EMA waived the obligation to conduct paediatric studies for over 600 products.[63] [64]

Table 1. Agreed, completed PIPs, authorised paediatric medicines by area

Therapeutic area	Number of agreed PIPs	Number of completed PIPs	Completed/ agreed PIPs	Number of authorisations of paediatric indications
Anaesthesiology	3	0	0%	0
Cardiovascular diseases	48	9	19%	6
Dermatology	33	5	15%	5
Diagnostics	13	2	15.4%	1
Gynaecology	12	3	25%	1

59 https://www.ema.europa.eu/en/committees/paediatric-committee-pdco
60 Communication from the Commission (2014C 338/01).
61 Section 3 of the Commission five-year report.
62 Agency's 10 years report, section 3.1, 10 years of the EU paediatric regulation (COM(2017)626) and annual reports from the Agency.
63 Ibid.
64 Under Article 11 of the Paediatric Regulation, a waiver can be agreed if the products may be inefficient or unsafe in children, if the disease they intend to treat does not exist in children, or if the product would not bring a significant therapeutic benefit compared with an existing treatment.

Endocrinology/metabolic diseases	70	7	10%	6
Gastroenterology/hepatology	33	5	15%	4
Haematology	46	3	6.5%	1
Transplantation	10	2	20%	1
Immunology/rheumatology	46	14	30.4%	8
Ophthalmology	17	2	12%	2
Vaccines	37	9	24.3%	9
Psychiatry	17	2	12%	2
Neurology	45	3	7%	2
Infectious diseases	96	14	15%	14
Neonatology/paediatric intensive care	16	1	6%	1
Oncology	83	7	10%	2
Pain	9	11	1%	0
Pneumonology/allergy	35*	7	20%	6
Uro-nephrology	16	1	6%	0
Orthopaedic diseases	9	1	11%	0
Allergens*	114	0	0%	0
Total	**808**	**98**	**12%**	**71**

Note: *Allergens PIPs assessed in 2010-2011 due to a change in regulation in Germany are listed separately here.
Source: EMA database (PedRA)

Nearly all PIPs for new medicines that are linked to an adult development include a delay in the implementation of one or more measures of the PIP (deferrals) until sufficient data on safety and efficacy are available in adults or in older age-groups. To verify companies' compliance with the agreed deferrals, marketing authorisation holders are required to submit annual reports to the Agency.[65] The list of companies that have not submitted one or more annual report(s) is published annually by the Commission on the basis of an EMA report (3 in 2018 and 2017, 8 in 2016, 11 in 2015).[66]

The agreed PIPs have had a direct effect on clinical research in the EU. They have resulted in more clinical trials in Europe. For instance, 12.4% of all clinical trials included children in 2016.

The Agency provides scientific advice (SA) on paediatric matters free of charge[67], and in 2018 it reached 25% of the total of 634 pieces of advice provided by EMA.[68]

More medicines for children

By 2018 there were over 200 new centrally authorised medicines authorised for use in children[69], and 6 PUMA authorisations had been granted by that time.[70] In addition, before

65 Article 34.4 of the Paediatric Regulation.
66 https://ec.europa.eu/health/human-use/paediatric-medicines_en
67 Article 26 of the Paediatric Regulation.
68 Report from the Agency to the European Commission 2018
69 Including new paediatric pharmaceutical formulations and indications.
70 EMA, 10-year report, section 1.1 and annual reports from the Agency.

the Regulation was introduced, the competent authorities completed assessments of more than 19 000 reports on paediatric studies (concerning 1000 active substances).[71] This resulted in 45 central and 2219 national reassessments, leading to about 140 updates of the product information and 16 new paediatric indications.

In response to a survey that provided input into the Commission's 10-year report, the majority of respondents estimated that the increase in the number of medicines available was in the 5-10% range. As regards prescription habits, 58% of respondents said that as a result of the Regulation practitioners were increasingly prescribing approved medicines according to their licensed indication for children.

Rewards

By 2016, more than 40 medicinal products had been granted an SPC extension by the national patent offices in one or more Member States, resulting in over 500 national extensions;[72] eight products had obtained the orphan reward of two additional years of market exclusivity until the end of 2018.[73]

Monitoring obligations

Reports under the Orphan Regulation

Article 10 of the Orphan Regulation required the Commission to publish a general report on the experience acquired from applying this Regulation, to include an account of the public health benefits.[74]

Article 9 of the Orphan Regulation obliges the Commission to publish a regular detailed inventory of all incentives provided by the EU and its Member States to support research, development and availability of orphan medicines. Since 2000, the Commission has published three such reports.[75] They have highlighted the steady increase in the number of requests for orphan designations over the years, showing the growing interest in this field. The orphan designation has been a requirement for Framework Programme funding since 2009. Both the number of orphan medicines applications submitted and the number of designations granted by the Commission rose by over 50% over 2009-2015, in comparison with 2000-2008.

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71 Articles 45 and 46 of the Paediatric Regulation.

72 Commission 10-year report.

73 EMA annual reports to the European Commission, https://ec.europa.eu/health/human-use/paediatric-medicines_en.

74 Commission Staff Working Document on the experience acquired as a result of the application of Regulation (EC) No 141/2000 on orphan medicinal products and account of the public health benefits obtained

75 Inventory of Union and Member State incentives to support research into, and the development and availability of, orphan medicinal products: 2015, 2005, 2002.

In line with Article 5(10), the sponsors of orphan designations are obliged to submit to the Agency an annual report on the state of development of the designated medicinal products. However, despite receiving this information, the Agency's Committee for Orphan Medicinal Products is not formally obliged to evaluate these reports.

Reports under the Paediatric Regulation

Article 50 of the Paediatric Regulation states that the Commission must report to the European Parliament and to the Council, 5 and 10 years respectively after the application of the legislation, on the experience acquired with that legislation.[76] These reports have been accompanied by extensive reports from the Agency to the Commission.[77]

The same article also requires the Commission, on the basis of information received from the Agency, to make public a list of the companies and products that have benefited from any of the rewards and incentives set out in this Regulation. This list includes the companies that have failed to comply with any of the obligations laid down in this Regulation. Companies discontinuing the placing on the market of a paediatric product/a paediatric indication must inform the Agency, which then makes this information public (Article 35). Further reporting obligations in the event of infringement of the Regulations' provisions are set out in Article 49 of the Paediatric Regulation.

4. METHOD

For the purpose of this evaluation, a Roadmap[78] was published on 11 December 2017 for a four-week period. Feedback was received from 23 stakeholders from business associations, companies, public authorities, NGOs, academic/research institutions, 5 from EU citizens and 2 from non-EU citizens.

4.1 Data gathering, methodology and analysis

A wide range of data sources have been used to collect evidence to answer the evaluation questions. Stakeholders' views were gathered through open public consultations and targeted consultation activities, including several workshops.[79] [80] All stakeholder groups were reached, and the risk of receiving incomplete or biased information was mitigated by

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76 Better Medicines for Children From Concept to Reality.
State of Paediatric Medicines in the EU, 10 years of the EU Paediatric Regulation.

77 General report on the experience acquired as a result of the application of the Paediatric Regulation (5-year Report to the European Commission, July 2012);
General report on the experience acquired as a result of the application of the Paediatric Regulation (10-year Report to the European Commission, August 2017).

78 Roadmap for the evaluation of the legislation on medicines for children and rare diseases (medicines for special populations)

79 Multi-stakeholder workshop held at the Agency on 20 March 2018.

80 Conference organised by the Commission, 'Medicines for Rare Diseases and Children: Learning from the Past, Looking to the Future'. 17 June 2019.

triangulating different sources of information, including multiple stakeholders, juxtaposing divergent viewpoints, and by providing the relevant factual information where possible.

Two independent studies were commissioned to support this evaluation, referred to in what follows as the 'orphan study'[81] and the 'paediatric study'.[82] In addition, the outcomes of an independent study on the impact of the pharmaceutical incentives were also used.[83]

The methodologies used in the orphan study included a **systematic review** of the peer-reviewed and grey literature, a **portfolio analysis** of the data on all designated and authorised orphan medicines (provided by **the Agency**[84]**),** as well as sales data (provided by **IQVIA and MPA Business Services**[85]**)** and a high-level **cost-benefit analysis**. The study included targeted consultations, conducted by means of surveys and interviews, involving five distinct groups of stakeholders:

1) national public authorities in EU Member States,

2) developers of innovative medicinal products,

3) developers of generic medicines,

4) patient and consumer organisations, and

5) Academic researchers and experts.[86]

The paediatric study focused on the Regulation's economic impact. An **analysis** of the **regulatory costs** and the indirect and direct **economic and social benefits** was performed. It included a **systematic review** of peer-reviewed and grey literature, a consultation of interested parties and a Delphi analysis.

A study on the economic impact of the supplementary protection certificates, pharmaceutical incentives and rewards in Europe provided additional findings which fed into the evaluation.[87]

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81 Study to support the evaluation of the EU Orphan Regulation, final report, July 2019).

82 Study on the economic impact of the Paediatric Regulation, including its rewards and incentives (2016).

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

84 Aggregated data on uptake and costs of incentives relating to the EU Orphan Regulation were provided.

85 IQVIA is a contract research and analytical services organisation that collects data including global pharmaceutical sales data (https://www.iqvia.com/). MPA Business Services is a business intelligence and market research company for the pharmaceutical and healthcare industry. It provides services including patent analytics services (http://mpasearch.co.uk/).

86 See the abstract of the Orphan study (2019).

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

A synopsis report summarising all activities carried out as part of stakeholder consultations, and their results, is provided in Annex 2.

Overall, the Commission agreed with the conclusions of these studies, despite the methodological limitations described below. The only exception was the result of the cost-benefit analysis for the pharmaceutical industry.[88] The Commission did not agree with the calculations performed by the contractor, and refined the cost-benefit analysis further by adding a competitive profit margin of 10% of the 'net' turnover (i.e. turnover minus the orphan exclusivity share).[89] For more details of the methodological aspects of the studies, please refer to Annex 3 of this report.

In addition to the above-mentioned studies, use was made of:

- the reports from the Commission to the European Parliament and the Council on the 5 and 10 years of implementation of the Paediatric Regulation[90],
- technical reports from the Agency to the Commission on the experience acquired as a result of the application of the Paediatric Regulation after 5 and 10 years of its application[91], and
- yearly reports from the Agency[92] on how the legislation's various provisions had performed.

4.2. Limitations and robustness of the findings

As regards the orphan study, the shortcomings and challenges listed below should be taken into account.

- Since there was no impact assessment for the Orphan Regulation, the baseline for the intervention had to be constructed retroactively.

- For this baseline, the concept of 'orphan-likes' was established, referring to products authorised before the Orphan Regulation for the treatment of rare diseases took effect. The concept is based on the following process. A list of US orphan medicinal products was obtained from the FDA's website. Their trade names were then matched with product names listed in the IQVIA database. If the trade name was a single word, an exact match with the first word of the product name was

88 Section 8.2.2. of the Orphan study report (2019).

89 The contractor had referred to 'normal profit margins' without quantifying them (and *de facto* counting profits as costs). See, for further explanation, Chapter 5.2.1. of this SWD.

90 Better Medicines for Children, From Concept to Reality;
State of Paediatric Medicines in the EU 10 years of the EU Paediatric Regulation.

91 General report on the experience acquired as a result of the application of the Paediatric Regulation (5-year Report to the European Commission, July 2012);
General report on the experience acquired as a result of the application of the Paediatric Regulation (10-year Report to the European Commission, August 2017)

92 https://ec.europa.eu/health/human-use/paediatric-medicines_en

counted. If the trade name consisted of two words, a match with the first two words of the product name was counted, and so on, depending on the number of words in the trade name of a US orphan medicinal product. All identified products are assumed to be 'orphan-like products'. Branded products were identified on the basis of a trade name, but they may also have been marketed under different trade names in different countries. This means that the volumes of such products may have been underestimated, which would have affected sales data.

- Overall, the assessment has probably:
    - overestimated costs (per quality-adjusted life year, QALY), as some orphans can be assumed to see generic/biosimilar entry in the longer run;
    - underestimated the increased availability, as more mature markets will see products available in more national jurisdictions, associated with product launch sequencing and possible generic/biosimilar entry over time;
    - failed to analyse generic competition in its entirety. This is because the estimate of the orphan reward (calculated based on price drops following generic/biosimilar entry) is tentative, given the timing of the evaluation; so far, only a limited set of orphans have lost market exclusivity.

- R&D costs of orphan medicines for developers had to be estimated on the basis of information in relevant literature, as sponsors of orphan medicines were unwilling or unable to provide these costs. Most R&D *funding* through EU programmes in basic and translational research, including research to develop orphan medicines, came from the sixth and seventh EU Framework Programmes for Research, Technological Development and Innovation (2002–2006 and 2007–2013), and Horizon 2020 (2014-2020). In addition to these EU programmes and initiatives, it is worth noting that over 90% of EU public funding for health research comes from the Member States. Although the available data provide some insight into the level of activity and funding, it has not been possible to produce accurate estimates of overall research funding for rare diseases in the EU; in this respect, the situation of rare diseases is similar to that of almost all other types of diseases. This is partly because, while some research programmes or projects are very clearly designed to improve understanding of rare diseases or develop treatments for them, others may be much more fundamental in nature. The CORDIS database contains information on EU-funded research projects, but there is no single database containing information from national funders. Rare diseases differ in this respect from several other research areas.

As regards the use of the IQVIA database to assess the Regulation's effectiveness and efficiency, the following limitations applied:

- The research team only had access to revenue and volume data for 2008 (first quarter) to 2017 (third quarter) for EEA countries, excluding Cyprus, Malta, Denmark, Iceland and Liechtenstein. The dataset provides only partial information (retail turnover) for the Netherlands, Latvia, Greece, Luxembourg and Estonia. Finally, the dataset presents combined data (no distinction between hospital and retail data) in the case of Slovenia.
- Revenues are based on list prices. In reality, the actual prices may be different, owing to price negotiations between companies and payers, which are usually confidential.
- The supply of orphan medicines may have been underestimated, given the specific sampling issues applicable to low-volume products (e.g. when a sample of pharmacies is used to estimate retail sales) or the possible use of direct import schemes ('named patient basis'), which are not captured through nationally operating wholesalers.

These limitations affected the calculations to establish availability and companies' sales revenues and thus the findings presented in the effectiveness and efficiency sections of the staff working document (SWD).

The *paediatric study* had the following limitations:

- Since it often takes over 10 years to develop a medicine, some of the provisions introduced by the legislation are only just starting to yield the expected results (such as the number of finalised paediatric investigation plans, PIPs). This means it was not possible to collect representative data for all provisions.
- For effectiveness in particular, it has not always been possible to provide data before 2017 because publically available data were not up to date. Data were updated when made available from a publicly accessible source, such as the yearly Agency reports to the Commission.
- For efficiency, the costs incurred in drawing up a PIP were estimated, as they are based on voluntary self-reporting by organisations. Furthermore, as many clinical trials are mixed trials, respondents may have had difficulties in correctly reporting the costs of the paediatric part only. The data provided may therefore have been over- or underestimated, affecting the representativeness of the sample.
- For efficiency, several assumptions were made in determining the value of the basket of medicinal products. These are linked to:
  (1) the variability of the year in which the rewards for the products selected were granted;
  (2) the variability of the Member States in which the rewards were granted;
  (3) the impossibility of determining the impact of generic entry in some Member States; and
  (4) the different dosages and presentations of the same product available in

various Member States.
Triangulations of information and extrapolations were used in the analysis to ensure the robustness of the findings.

- For efficiency, the costs incurred by regulatory authorities could not be estimated in detail.

5. ANALYSIS AND ANSWERS TO THE EVALUATION QUESTIONS

5.1 EFFECTIVENESS

Main findings

Orphan Regulation

The various incentives provided by the *Orphan* Regulation have spurred on the development of new treatments for rare diseases. However, not all orphan products authorised under the Regulation are the direct results of such incentives. Of the 131 orphan medicines authorised in the EU since 2000, the Orphan Regulation is estimated to be responsible for at least 8-24 new ones. The remaining 107-113 products were made available more quickly, and reached more people across the EU, than before the Regulation took effect. SMEs, in particular, benefited from protocol assistance and fee reduction. However, in many cases charitable foundations and academic institutions are not eligible for fee reduction because of difficulties in meeting the 'SME criteria'.

The development of new orphan medicines addressed some of the rarest diseases. However, the tools provided by the Orphan Regulation have not done enough to direct the development in areas of greatest 'unmet medical need'. The Regulation has not been sufficiently effective to catalyse the clinical development to areas where there are no treatments yet. At the same time, the number of treatment options is expanding in specific areas, such as oncology. Here, the market is starting to look more and more like that of the non-orphans.

Stakeholders have questioned whether the currently used prevalence threshold of 5 in 10,000 is an appropriate criterion. The criterion of 'insufficient return on investment' has only been used once, as companies seem to fear the possible shortening of the market exclusivity period to six years for economically successful products, when reassessed after five years.

Marketing authorisation of orphan medicines at EU level (availability) has not translated into accessibility of the authorised medicines for patients in *all* Member States. Access to orphan medicines varies considerably across Member States, mainly owing to factors beyond the Regulation's ambit, such as different national pricing and reimbursement

systems, companies' strategic decisions on market launch, and the role of healthcare providers.

Paediatric Regulation

The Paediatric Regulation has led to an increase in clinical research involving children and in medicinal products specifically authorised for them, as well as to improvements in the level of information available on such products. However, these advances have been more substantial in cases where a parallel adult medicine development was ongoing.

The Regulation has no effective instruments to direct research and development toward specific therapeutic areas and it works better in areas where the needs of adult and paediatric patients overlap. The SPC extension is of particular relevance, economically speaking, to products with high sales in adults (blockbusters). Accordingly, it may not be successful in incentivising the development of medicines in line with children's most pressing needs. Neither regulation has proven effective in boosting the development of innovative medicines for children with rare diseases.

Little use has been made of the other rewards provided by the Paediatric Regulation, the orphan reward, or the PUMA (paediatric use marketing authorisation) scheme.

The analysis showed that the Regulation has had a positive effect overall in gradually helping to reduce off-label use of adult medicines in children. This result is however impacted by external factors, such as companies' launch decisions, the reimbursement and pricing decisions taken by national competent authorities, and doctors' patterns of prescription.

How effective the two Regulations have been can be assessed from the relation between the effects observed and the stated objectives. To this end, this chapter assesses the extent to which the two Regulations have helped boost research, development and authorisation of remedies for rare diseases and medicines for children. It also examines whether the products developed under the Regulations serve patients' needs effectively, in terms both of addressing unmet needs and of timely availability across the EU. Finally, it examines the Regulations' impact on R&D and competitiveness.

5.1.1 – The impact on research and development for orphan medicines

The Regulation has had a substantial impact on R&D in the field of orphan medicines in the EU. Between 2000 and 2017, 1956 designations were granted and 142 orphan medicines were authorised (11 were subsequently withdrawn, thus leaving 131 on the market). The increasing number of orphan designations reflect the industry's growing interest in developing orphan medicines. In the first three years following the adoption of the Orphan Regulation, between 72 and 80 applications for designations were submitted

annually (see Figure 6), instead of 5-12, as was initially estimated for that period. In recent years, the number has exceeded 200 applications per year.

The 1956 designations covered 698 different indications. They included 637 treatments (91%), 53 products used for prevention (8%), and 8 products used for diagnosis (1%).

However, only about 5% of orphan products under development (designations) went on to be authorised as orphan medicinal products.

By the end of the first five years, 22 orphan medicines had been authorised for the treatment of 20 different life-threatening or chronically debilitating rare diseases. An upward trend can be seen from the average numbers of orphan marketing authorisations in three six-year periods: 3.7 per year in 2000-2005, 7.8 per year in 2006-2011 and 12.2 per year in 2012-2017. At the same time, the US saw an even more impressive increase (from 17 in 2008 to 77 in 2017).[93]

Figure 6: Number of applications submitted, designations granted and authorised orphan medicines (2000 – 2017)

Source: Agency (2018)

93 US Government Accountability Office Report on orphan drugs (November 2018), p. 23.

To estimate what proportion of the orphan medicines authorised in the EU can be attributed to the EU Orphan Regulation, the trend in marketing authorisations for orphan medicines from 2000 to 2017 was compared with the general market trend in pharmaceutical product development. This analysis[94] shows that since 2011, the number of marketing authorisations for orphan medicines has not only grown over time, but has grown substantially faster than those for non-orphan medicines. Using these data, it was estimated that of the 131 orphan medicines authorised in the EU, between 18 and 24 (almost 20%) were developed as a result of the legislation. If orphan medicines had followed the same market trend as non-orphan medicines, then only about 107 to 113 would have been authorised.[95] Having said that, we have to acknowledge that there is no best available statistical methodology to assess how the legislations impact directly the development of medicines due to the lack of sufficient data. Therefore, the above mentioned figures are indicative and may be under representative.

Table 2 Average number of new marketing authorisations per year

Year	Orphan medical products	Increase (%)	Non-orphan medical products	Increase (%)
2000-2005	3.7		28.8	
2006-2011	7.8	111	63.8	122
2012-2017	12.2	56	68.3	7

Source: Orphan Study Report

Compared to the EU, the US has higher annual figures for both designations and marketing authorisations for orphan medicines. Differences in the eligibility criteria for obtaining an orphan designation in the EU, US and Japan also result in different percentages of designated orphans finally authorised in these regions (8% of successful marketing authorisations from orphan designations were identified in the EU, compared to 15% in the US, and 65% in Japan).[96] [97]

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 medicines in the US.

Under Japanese legislation, only medicines with a strong chance of approval are designated as orphan drugs. This may account for Japan's high approval to designation ratio.

94 For all calculations, see Section 1.4.2. of Annex 3.
95 Idem.
96 Murakami M and Narukawa M, Drug Discovery Today, (2016), 21(4):544-549.
97 See also Annex 7 (International context).

In 2017, the FDA took several steps to improve the consistency and efficiency of its evaluations to verify the accuracy of manufacturers' claims in their orphan designation applications. These steps included introducing a standard review template and providing guidance on completing it.[98] No comparable analysis of the consistency of the EMA assessments was performed in connection with this report.

Role of incentives under the Orphan Regulation

The average additional protection offered by the **market exclusivity reward** was calculated at 3.4 years. The economic value of this reward, calculated for a limited sample of products, averaged 30% of total turnover. For around half of the analysed sample, market exclusivity was the last protection to expiry.[99]

Developers pointed out that companies' decisions to launch new products in the EU were influenced by the possibility of market exclusivity laid down by the Regulation and the legal certainty it provides.[100] They considered market exclusivity to be the main incentive[101], which, together with orphan designation, would enable fledgling companies to attract venture capital.

A comparison with the US nuanced these statements. In this context, developers underlined 'non-incentive' drivers of growth in orphan medicines, such as the ability to demand high prices. The same report noted that marketing exclusivity was having a declining impact on protecting orphan medicinal products from competition in the US.[102]

Market exclusivity is not the only major incentive. The EU and its Member States, within their respective spheres of competence, provide *other* incentives for developing medicines for rare diseases. While the EU supports research, some Member States provide tax incentives, for instance.[103]

Although developers considered the two-year **paediatric extension** to the market exclusivity to be very important,[104] only a few medicinal products had actually benefited from this reward.[105]

The specific form of scientific advice offered by the Agency under the Regulation, known as **protocol assistance,** has significantly increased over time: from 4 in 2000 to over 125

98 US Government Accountability Office Report on orphan drugs (November 2018), p. 7.
99 See Chapter 5.2 and Annex 3 of this SWD.
100 Section 10.2 of Orphan study report (2019).
101 A natural monopoly that could give pharmaceutical companies a very strong bargaining position in price negotiations with payers. (Section 1.1 of the Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe (2018)).
102 US Government Accountability Office Report on orphan drugs (November 2018), pp. 31-32.
103 Inventory of EU and national incentives to support research and development.
104 Section 7.1.1. of the Orphan study report (2019).
105 An analysis of this reward will be provided in Chapter 5.1.3. of this SWD.

requests per year in 2017. While the information available does not allow any firm conclusions to be drawn[106] as regards the role of protocol assistance, several studies show a strong association between compliance with protocol assistance recommendations and marketing authorisation success for orphan medicines. Targeted surveys have indicated that protocol assistance is very important for industry, especially for relatively inexperienced developers. The growing share of small and medium-sized enterprises (SMEs) among applications for protocol assistance (50% in 2017) tallies with the observation that SMEs now account for around half of all designations annually.[107]

The **fee reduction** is considered important by developers, especially SMEs, as fees are waived completely for this group. It was noted, though, that for some sponsors, such as charitable foundations and academic institutions, it can be difficult to meet the requirements for SME status[108] and for them the Agency fees can still be significant. There were no data to determine whether these fee reductions, compared to the overall costs of R&D, have made an appreciable impact on the number of products under development. It is not known either how often these fees do represent a real barrier to potential sponsors.

The effectiveness of the incentives also depends on many other contextual factors that influence the outcomes of clinical development of orphan medicines, such as the experience of the developer, market and product characteristics, and the stage of development of the product. Even the best designed intervention may not succeed if it is not supported by progress in basic research or new scientific leads for product development. It was clear from the beginning that market exclusivity would not be the only main incentive, and that it would be up to the EU and the Member States to provide other incentives for developing orphan medicines, such as support for research.

Moreover, the effects of individual incentives cannot be isolated from each other, nor can the effectiveness of incentives offered by the EU Orphan Regulation be seen as separate from that of incentives offered by similar regulations in other jurisdictions such as the US.[109]

In the international comparison of incentives, the duration of market exclusivity (10 years in the EU 10, vs. 7 years in the US) is the most striking difference. However, other jurisdictions (US, Japan) also provide tax incentives, whereas the EU does not.[110] In this

106 Section 7.1.1. of the Orphan study report (2019).

107 Section 7.5.2. of the Orphan Study report (2019).

108 SMEs are micro, small and medium-sized enterprises (companies employing fewer than 250 people, with an annual turnover not exceeding EUR 50 million, and/or an annual balance sheet total not exceeding EUR 42 million.

109 Although in a recent US report developers downplayed the significance of US incentives for developing orphan drugs (US Government Accountability Office Report on orphan drugs, November 2018, p. 31).

110 See also Annex 7 for a comparison of incentives offered by the EU, US and Japanese regulatory frameworks.

respect, the US market may be regarded as quite attractive; most of the revenues from orphan medicines are earned in the US alone.[111]

5.1.2 – The impact on unmet needs and timely availability for orphan medicines

The Orphan and the Paediatric Regulation were designed to address the unmet medical needs of patients suffering from rare diseases and of children. However, the concept of unmet medical need has not so far been standardised among patients, industry, regulators, HTA bodies and payers.[112] [113] For the purpose of this analysis, the concept of unmet medical need was therefore operationalised. It was assessed whether, and to what extent, the Regulations have contributed to the development and availability of orphan drugs and paediatric medicines, and what therapeutic areas are covered by these medicines.

The extent to which new orphan medicines target conditions for which no alternative treatments exist and the rarity of conditions for which designations were granted were also considered. Finally, it was assessed whether EU patients have access to such medicines. After all, there is no point in developing treatments if patients have no access to them.

Product development in different therapeutic areas and indications

Since 2000, almost all therapeutic areas have been covered by authorised orphan medicines. Only in the categories of genito-urinary tract conditions and sex hormones and anti-parasitic products have no medicines yet been authorised.[114] Despite this development, 95% of rare diseases still have no treatment option; the situation in the US is very similar.[115] [116] Furthermore, of the 142 authorised orphan medicines, only 28% target diseases for which there were no alternative treatments.

To compare this to the situation *before* the Orphan Regulation came into force, 70 medicinal products already authorised as orphans in the US were available in at least one

[111] 70% of global revenues from orphan medicines come from the US (Orphan Drug Report 2019, EvaluatePharma). See also Chapter 5.2. of this SWD.

[112] The concept was important for decision making. Value in Health, Volume 22, Issue 11, November 2019, pp. 1275-1282;

[113] See, *inter alia*, the outcomes of the European Commission Conference on 'Medicines for Rare Diseases and Children: Learning from the Past, Looking to the Future' (June 2019) – details in Annex 2 (Synopsis report).

[114] See Section 5.4.1 of the Orphan study report (2019).

[115] Orphan products, like any medicinal product, must be clinically tested before attaining marketing authorisation. While the legislation may act as enabler, it cannot substitute inherent research challenges that affect product development.

[116] US Government Accountability Office Report on orphan drugs, November 2018.

Member State in 2000.[117] Most of these 70 products were substances acting on the immune system.[118]

In the years immediately after the Regulation's introduction, the annual number of new orphan indications declined rapidly. While in 2001 78% of orphan designations were for new indications (i.e. indications for which no products had been authorised), in recent years the figure fell to less than one in five (<20%) designations.

For those indications where products have already been authorised, a product needs to demonstrate significant benefit over existing treatment options to be maintained as an orphan product and to receive market exclusivity. Owing to the increasing number of orphan medicines authorised, more and more products need to demonstrate significant benefit. An analysis performed in 2018 on products authorised between 2000 and 2015 showed that demonstration of significant benefit was required in 64% of designations and for 73% of products at the time of marketing authorisation. This indicates that the EU Orphan Regulation is becoming less effective in directing research to areas where there are no treatments yet, and product development tends to cluster around certain (more profitable) therapeutic areas. Consequently, the number of treatment options is expanding for some conditions, and the market is starting to look more like the one for 'standard' medicines.

An area which has attracted considerable attention, for instance, is anti-cancer treatments, accounting for around a third of all designations and authorised products so far. As treatments for rare cancers often have broader applicability across a range of other cancers - some of which may not be considered rare - these products may have a higher profit potential. A similar degree of concentration has been observed in the US, where a large share of orphan drug marketing approvals (42%) were in oncology between 2008 and 2017.[119]

Stakeholder consultations indicate that the accelerated development of new treatments in oncology can be explained by a better understanding of the natural history of disease and of the molecular pathways it involves.

The lack of development in certain therapeutic areas, according to the developers surveyed, may be attributable to the fact that companies tend to focus on certain areas of disease, on a lack of scientific expertise, and on a lack of basic research in certain fields. Other possible reasons are insufficient knowledge of disease mechanisms and poor understanding of the

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117 See Chapter 2 (Baseline and points of comparison) of this SWD. These 'orphan-likes' were not formally labelled as orphan products in the EU, but have likely also served the rare disease population in the EU.

118 Such as endocrine therapy, immunostimulants or immunosuppressants.
See Section 2.2. of the Orphan study report (2019).

119 US Government Accountability Office Report on orphan drugs, November 2018, p. 23.

underlying biology. On top of this, for ultra-rare diseases (affecting less than one patient in 10,000) the study of patients' clinical symptoms and the conduct of effective clinical trials is constrained by the small number of patients available for robust statistical analyses. The same barriers to developing orphan medicines have also been identified in the US.[120]

The Regulation has therefore not met its aim of addressing unmet medical needs in all therapeutic areas.

Development of follow-on products

Granting orphan market exclusivity to a given product could potentially constitute a barrier to developing follow-on products of an orphan indication covered by the first authorised product. If that were the case, patients unable to benefit sufficiently from the first medicine could potentially be deprived of additional treatment options.

In theory, the EU Orphan Regulation contains provisions to mitigate the impact of market exclusivity on the development of follow-on products. First, the market exclusivity for orphan medicines only extends market protection against competition by 'similar medicines with similar indications'. A similar medicine is understood to contain 'an identical active substance, or an active substance with the same principal molecular structural features and which acts via the same mechanism'.[121]

A product that contains a different active substance, or that acts on a different molecular pathway is therefore not prevented from entering the market alongside the original product, even if the latter is still under market exclusivity. In the case of biological medicines including advanced therapy medicinal products (ATMPs), whose principle molecular structural features cannot be identified, the similarity between two active substances is assessed on the basis of their biological and functional characteristics.[122] However, to be eligible for an orphan designation itself, that product would need to demonstrate significant benefit over the treatment already authorised.

It could therefore be argued that the fact that a competing product has obtained a marketing authorisation influences decisions on whether to continue the development of a product. For 82% of orphan indications where there is at least one authorised orphan medicine, there is no other authorised orphan medicine (yet). Also, in a market that is inherently small, developers may question whether there is sufficient willingness among patients and

120 Idem, p. 30.

121 Article 3C of Commission Regulation (EC) No 847/2000 of 27 April 2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts 'similar medicinal product' and 'clinical superiority'. Available at https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/reg_2000_847/reg_2000_847_en.pdf. Accessed 13 January 2019.

122 Owing to major developments in the field of ATMPs, the definition of 'similar medicinal product' was amended in 2018 by Commission Regulation (EC) 2018/781.

prescribers to switch to another product. However, most developers surveyed reported that competition with another organisation, whether likely or already existing, does not lead to the suspension, termination, refocusing or delay of new or ongoing R&D.

Another study[123] showed that the likelihood of a rare disorder with an approved orphan medicine obtaining at least one follow-on orphan medicine was strongly associated with the number of people affected by this disease, turnover of the first orphan product, specific disease class, the extent of scientific knowledge about the disease, and whether it starts during childhood or later on. In areas where there are no follow-on orphan medicines, the main reasons seemed to be the time needed to develop follow-on products and market size, rather than any 'monopolies' created by market exclusivity.

Rarity of conditions and 'insufficient return on investment'

Around a third of authorised orphan products are for treatments with a prevalence of less than 0.5 in 10,000. These are mainly products for the treatment of diseases affecting the musculoskeletal system, but also some rare forms of cancer. A recent study shows that 84.5% of analysed rare diseases have a very low prevalence (less than 1 in 1,000,000). However, most of the *population* burden of rare diseases is attributable to the 4.2% diseases in the most common prevalence range (1–5 per 10,000).[124]

Although the Orphan Regulation helped promote the development of products tackling some of the rarest diseases, where the market potential is limited, according to some stakeholders (patients' organisations, national authorities, and researchers), it also stimulated development in areas where sufficient market stimuli already exist. Stakeholders questioned whether the prevalence threshold currently used of 5 in 10,000 is appropriate as a criterion. In this regard, it was argued that the expected use of a product in an underlying condition (once, repeated, life-long) has a decisive role and may also need to be taken into account during the assessment if the development of truly financially-unattractive areas is to be fostered (such as paediatric oncology). Hence, the question is raised whether a different method for calculating prevalence is needed or even a different criterion (the US and Japan, for instance, also use criteria based on absolute numbers of patients in these countries).

Moreover, a graduation/differentiation of the incentives to the magnitude of rarity or the scale of investment needed may enable incentives to be focused better on therapeutic areas that are neglected or where a bigger investment is necessary. It has been also suggested that using the rare disease registries project supported by the European Reference

[123] Brabers, Moors, Van Weely, & La De Vrueh, (2011) 'Does market exclusivity hinder the development of follow-on orphan medicinal products in Europe?' Orphanet J Rare Dis, 6: 59.

[124] Nguengang Wakap S, Lambert DM, Olry A, Rodwell C, Gueydan C, Lanneau V, et al. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. Eur J Hum Genet. 2019. 10.1038/s41431-019-0508-0.

Networks could help the Committee for Orphan Medicinal Products (COMP) access the best available data.

By the end of 2017, only one application had been received under the 'insufficient return on investment criterion', and that was subsequently withdrawn. According to the industry, the criterion's lack of success is due to the difficulty of estimating future investments and returns on that investment *a priori*, before the therapeutic indications for which the product may be used or the price at which it will be sold are clear. However, other stakeholders suggested that applications on the grounds of expectation of insufficient return on investment are absent for another reason, too; such an application could make sponsors of economically successful products vulnerable to reassessment. Reassessment could lead to the market exclusivity period being reduced to six years if the product were found to be sufficiently profitable. Antimicrobials, on the other hand, could have benefited from the incentives of the Orphan Regulation under the provision of 'insufficient return on investment'. The development of new medicines to replace ineffective antimicrobials seems to be inadequate to meet patients' needs.

Yet no novel antimicrobials have been developed to date. Arguably, the insufficient return on investment criterion in the Orphan Regulation could have been used, but developers have not had recourse to it. This lack of development was also recognised in a recent special report by the Court of Auditors in November 2019.[125] The question of how to address market failures affecting the provision of new antimicrobials should be further examined, in consultation with the Member States and other stakeholders.

In the US, a legal act[126] in 2012 created incentives for sponsors to bring to market antibacterial and antifungal drugs intended to treat serious or life-threatening infections. It allows the FDA to designate certain antimicrobial drugs as qualified infectious disease products. Through this designation, sponsors can profit from incentives to bring antibacterial and antifungal drugs for serious or life-threatening infections to market more rapidly and be granted a five-year extension of any exclusivity that the application qualifies for upon approval.

Availability of and access to orphan medicines

An analysis of IQVIA data indicated[127] that the Orphan Regulation has not only stimulated new development of orphan medicines, but has also helped **make them available faster in the EU**. It was estimated that orphan medicines became available on average nine months earlier than would have been the case without the Regulation.

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125 Special Report No 21/2019, 'Addressing antimicrobial resistance: progress in the animal sector, but this health threat remains a challenge for the EU' (European Court of Auditors, November 2019).

126 Generating Antibiotic Incentives Now (GAIN), part of the Food and Drug Administration Safety and Innovation Act (FDASIA).

127 For detailed calculations, see Section 1.4.2. of Annex 3.

In addition, the Orphan Regulation has also helped to made orphan medicines **more widely available**. The 142 orphan medicines authorised between 2000 and 2017 have helped up to 6.3 million patients in the EU, out of roughly 35 million European patients suffering from rare diseases. Before these medicines were authorised, there were no satisfactory treatment options authorised in the EU for 8 out of 20 rare conditions (40%). More than one million patients suffering from these orphan diseases in the EU were already benefiting from the availability of these new treatments by 2005.[128]

Since 2005, all orphan medicines have had to be authorised through the centralised marketing authorisation procedure. However, this has not ensured that *all* EU patients suffering from the same orphan disease automatically have the same choice of treatment. Not all centrally-authorised medicines are launched in all Member States: in some, access to orphan drugs is very limited.[129]

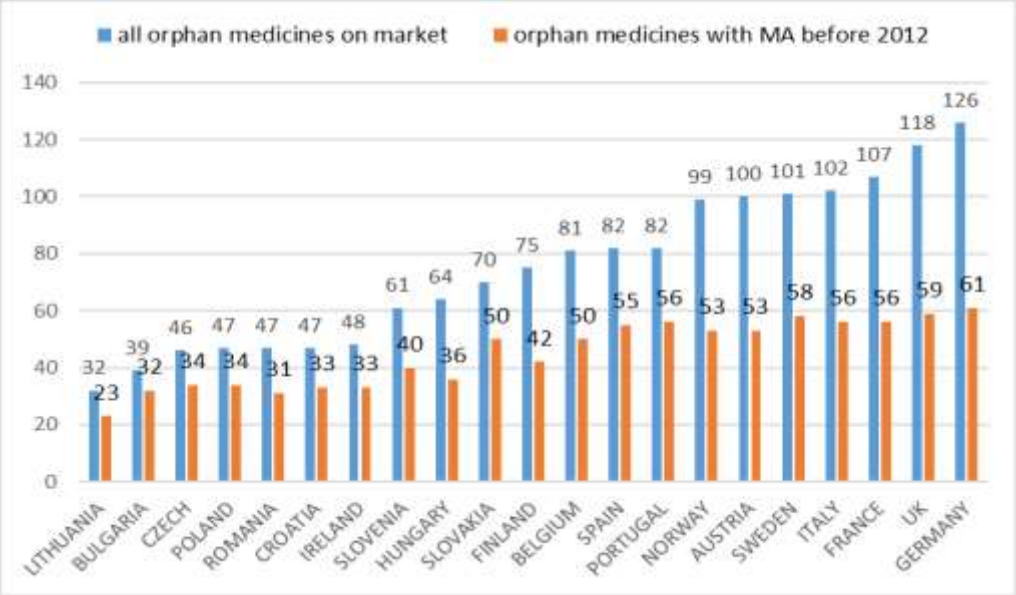
Countries such as Germany, the UK, France, Austria, Sweden and Italy have a high market uptake of orphan medicines, with more than 100 orphan drugs available (Figure 7).[130] This suggests that the market conditions in these countries may be favourable. In particular, measures taken by Member States in areas of national competence, such as reimbursement and pricing, corporate taxation, and healthcare provision, significantly affect the current availability of orphan medicines on the market.

[128] Commission Staff Working Document on the experience acquired with the Orphan Regulation from 2000 to 2005.

[129] Stakeholders suggested that, to improve overall availability and access, measures are needed that focus on greater alignment of pricing and reimbursement policies and procedures and on joint procurement and negotiation. Sections 6.2.3. and 9.5.2. of the Orphan study report (2019)).

[130] This was measured through IQVIA sales data (2008–2016), where any sales figure larger than zero is considered indicative of availability of a medicine on the market.

Figure 7:[131] Number of orphan medicines for which sales were observed in 2016 (IQVIA) by Member State



Several *external* factors influence availability and access to orphan medicines. Although these factors already existed in 2000, their role seems to be more prominent now in influencing availability and access to orphan medicines. The Orphan Regulation does not impose any obligation on marketing authorisation holders to market an authorised orphan medicine in all EU Member States. Indeed, a marketing authorisation holder may decide not to place a product on a particular market ('launch decision'), because it does not see it as commercially attractive; possible reasons are a small treatment population, existing competition, or treatment alternatives. Stakeholders have also pointed to concerns of parallel export.[132]

National pricing and reimbursement practices and policies also influence patients' access to orphan medicines. An example is the system of 'external reference pricing' by which a country determines the official 'price list' based on the prices averaged over a set of fixed reference countries. This system causes marketing authorisation holders to engage in strategic decision-making to maximise overall prices and results in 'cascaded' market entry, whereby some countries are more likely to see a rapid placement on the market than

[131] Source: analysis of IQVIA data in Section 6.2.1. of the Orphan study report (2019). This included withdrawn and expired orphan medicines.

[132] Parallel imports and exports of medicinal products are a lawful form of trade within the EU Single Market. However, in certain cases Member States may restrict parallel trade, as long as the measures are justified, reasonable and proportionate, to ensure a legitimate public interest. (https://europa.eu/rapid/press-release_IP-18-3459_en.htm).

others.[133] This is also linked to how much a country can pay, or is willing to pay, for a medicinal product.

Findings show[134] that companies tend to launch more medicinal products faster in wealthier countries with a higher GDP than in countries with lower GDP. The trend is stronger in countries with a larger population of potential patients.[135] This suggests that launch decisions are guided to some extent by market attractiveness.

Moreover, the frequently high prices of many orphan medicines, in particular, often mean that whether a patient can access a treatment also depends largely on whether it is fully reimbursed by the health system, or whether personal payments or co-payments are required.

'Payers'[136] also decide which products will be provided and paid for by the public healthcare system or health insurance funds, on the basis of national pricing and reimbursement policies often supported by health technology assessment[137] (HTA). A survey of NCAs indicated[138] that in most Member States there are no major differences in reimbursements between orphans and other medicines. In addition to or apart from the special regulations or policies on orphans, there are separate budgets, more relaxed assumptions or accepted levels of uncertainty in the HTA process, or managed entry agreements in some Member States.[139] [140] However, even once a decision has been taken to reimburse an orphan medicine, entirely or partially, differences in financing and reimbursement systems between Member States can influence whether and when patients are able to access a treatment.

Indeed, in many countries decision-making on reimbursement is often informed by the work of HTA agencies to establish cost-effectiveness.[141] Moreover, several countries have brought in 'managed entry agreements'. These agreements are used in the context of

133 See also Section 2.2 of the Study on the economic impact of the supplementary protection certificates, pharmaceutical incentives and rewards in Europe (2018).

134 Section 2.2 of the Study on the economic impact of the supplementary protection certificates, pharmaceutical incentives and rewards in Europe (2018).

135 Gross domestic product, measuring the overall size of an economy with derived indicators such as GDP per inhabitant (per capita). See also: https://ec.europa.eu/eurostat/statistics-explained/index.php/National_accounts_and_GDP

136 Health ministries are typically involved in laying down the policies and criteria that determine how public funds can be directed for pharmaceutical products.

137 A health technology assessment measures the added value of a new health technology compared to existing ones. Examples of health technologies include medicinal products, medical equipment, diagnostic and treatment methods, rehabilitation, and prevention methods (see also: https://ec.europa.eu/health/technology_assessment/overview_en).

138 See Section 6.2.2. of the Orphan study report (2019).

139 Sarnola, K. et al. Eur J Clin Pharmacol 74, 895–902 (2018).

140 Malinowski KP et al. Front. Pharmacol. 9:1263 (2018).

141 Section 9.5 of the Orphan study report (2019).

reimbursement for medicines whose evidence base is immature. They are designed to balance the need for speedy access to the health system for treatments addressing an important unmet medical need with the principle of maximising value for money and affordability.[142]

The methods used for HTA may vary and outcomes are dependent on national factors, such as the characteristics of the healthcare system and how the product is to be used in treatment. The draft Commission proposal on HTA[143] may provide a higher level of convergence in HTA methodologies and greater coherence between EU procedures for marketing authorisation and national procedures for the reimbursement of medicines.

Finally, access to orphan medicines can be influenced by health professionals' prescribing practices and habits. In fact, even when products are placed on a market by a marketing authorisation holder and the medicine is largely reimbursed, there is no guarantee that all patients will receive it. Reasons may include unfamiliarity with the disease/product and/or a lack of diagnostic capacity.[144] [145]

Unequal access to medicines, and particularly to orphan drugs, remains an issue today. The Regulation has only succeeded in part in providing the right tools to ensure that patients suffering from rare conditions have the same quality of treatment as any other patient, thanks to the development of more orphan medicines and their increased availability.

5.1.3 – The impact on research and development of paediatric medicines

More clinical research, more products and more information on paediatric medicines

The Paediatric Regulation has helped boost paediatric clinical research, increase availability of products with paediatric indications in the EU market and improve the information available about these medicines. The vast majority of stakeholders who responded to a public consultation[146] thought the Paediatric Regulation had had a positive impact in addressing the lack of medicines studied and developed appropriately for children.

142 Section 9.5.2 of the Orphan study report (2019).

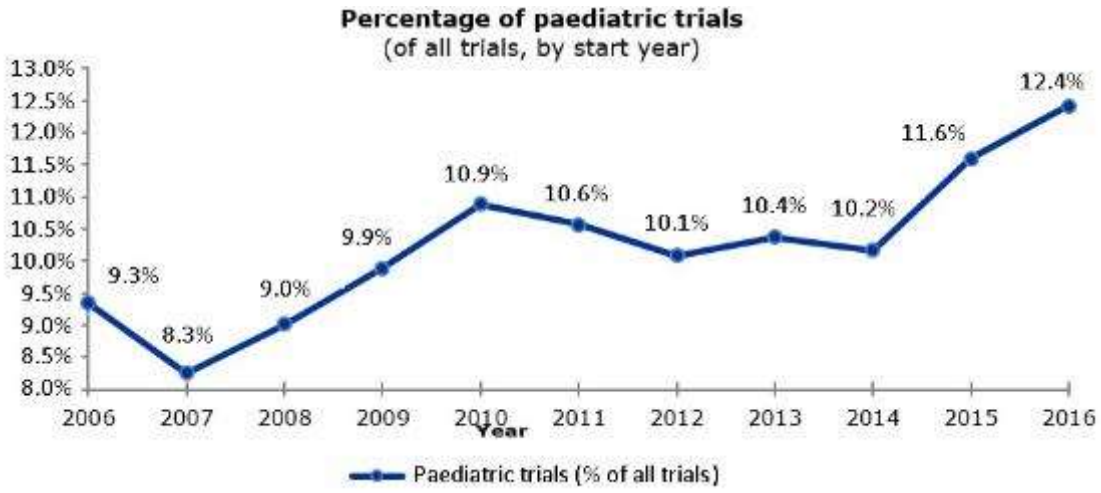
143 https://ec.europa.eu/health/technology_assessment/eu_cooperation_en

144 A doctor needs to be aware of the availability and potential benefits of a treatment before they can allow a prescription. Usually, this involves a form of codification in prescription guidelines developed by medical professional associations. Additionally, adequate capacity needs to be available to correctly diagnose a rare disease. These factors influence doctors' decisions when prescribing medicines for patients.

145 Section 6.2.2. of the Orphan study report (2019).

146 Replies to the public consultation on the Commission report on the Paediatric Regulation.

Figure 7: Proportion of clinical trials that include children



Source: 10 years of the EU Paediatric Regulation report, European Commission

Over 1000 PIPs had been agreed on by the end of 2018.[147] An agreement on a paediatric investigation plan means that companies need to invest in additional paediatric research. On average, every PIP includes around three clinical studies. These studies have led to an increase in paediatric trials as a percentage of all trials conducted in the EU, from around 8.3% (188 exclusively paediatric trials) in 2007 to 12.4% (473 exclusively paediatric trials) in 2016 (Figure 7).[148] They have also led to an increased use of scientific advice from 7.6% of the total items of advice provided by the Agency in 2007 to 24.4% of the total in 2016.[149] Importantly, clinical trials involving neonates (a particularly neglected paediatric subpopulation) were included in over a quarter of all the PIPs agreed on, often at the Agency's request.

By June 2018, about 18% of the PIPs agreed on had been completed, with a clear upward trend in recent years.[150] Over 60% were completed in 2013-2016.[151]

By 2016, 101 paediatric medicines and 99 new paediatric indications had been authorised centrally. For nationally-authorised products in the same period, 10 new paediatric medicines were authorised and 57 new paediatric indications approved.[152] The contribution made by the Regulation to these results can be estimated by comparing data collected from the three years preceding its application (2004-2006) with later periods when the

147 10 years of the EU paediatric regulation, report from the Commission to the European Parliament and the Council (COM(2017) 626, Section 3 and annual reports from the Agency.

148 10 years of the EU paediatric regulation, report from the Commission to the European Parliament and the Council (COM(2017) 626, Section 8 – source: EudraCT.

149 Section 3.5 of the Agency's 10 years report.

150 Idem.

151 10 years of the EU paediatric regulation, report from the Commission to the European Parliament and the Council (COM(2017) 626, Section 3.

152 Section 1.1 of the Agency 10 years report.

Regulation was fully operational and authorisation of all paediatric medicines was preceded by a PIP. From 2004 to 2006, 30 new medicines and indications were authorised for paediatric use. In 2012-2014 and 2014-2016, the figure rose to 63 and 74 respectively; in other words, the output had more than doubled.

Furthermore, the Agency and the national competent authorities had received around 19,000 reports on paediatric studies involving 1000 active substances that had been completed before the entry into force of the Paediatric Regulation.[153] These reports resulted in 45 central and 2219 national reassessments, leading to about 140 updates of product information and 16 new paediatric indications for products already authorised.[154]

The figures above concerning both clinical research in children and the authorisation of medicines for children match expectations and the best-case scenario described in the impact assessment, which predicted that within 10-15 years all patent-protected medicines would be studied in children (unless exempted from this obligation). However, given the long development time for medicines, particularly with complex and rare diseases, as is often the case with paediatric diseases, it could take up to 20 years before most products could be authorised for use in children.

While the main aim of the Paediatric Regulation is to ensure that every new adult medicine has been researched for its potential paediatric use, it should be borne in mind that by the end of 2017 the Agency had approved almost 500 waivers from the obligation to conduct a PIP (against the 1000 PIPs it had agreed on).[155] [156]

It is generally appropriate to waive paediatric studies if the target disease does not exist in children.[157] However, one cannot rule out the possibility that a compound, given its mechanism of action, may in some cases be beneficial to children, albeit for a different medical condition. This is particularly relevant in the field of oncology. While many paediatric cancers share biological similarities with adult cancers, they occur in different organs and are therefore usually classed as different conditions. The way the legislation is designed thus means that certain compounds which might be useful for children are not tested on them. The US, which had a similar problem, has recently introduced changes to its legislation.[158]

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153 Articles 45 and 46 of the Paediatric Regulation.

154 Chapter 2 of the Agency 10 years report.

155 Product-specific and class waivers 10 years report from the Agency (Section 3) and Commission 10-year report (Section 4).

156 In 2016, 486 were product-specific waivers. By 2018, the figure had risen to over 600 product-specific waivers.

157 Article 11 of the Paediatric Regulation.

158 The new US legislation, set to become fully applicable in 2020, will incorporate the concept of mechanism of action and observed changes in oncology drug development towards histology-independent indication. See: https://www.congress.gov/115/plaws/publ52/PLAW-115publ52.pdf

The Agency has tried to mitigate this issue through a review of its class waiver decision in 2015, revoking some automatic waivers for carcinomas.[159] Some advances have been observed since then. However, the progress made is not solely attributable to the review of the class waiver list. As paediatric development is global, the revision of the legislation in the US[160] may also have played a role. Moreover, the change in the class waiver list does not seem to have encouraged companies to submit voluntary PIPs for all the medicines concerned.[161]

The Regulation also delivers slowly because nearly all paediatric studies for new medicines that are linked to an adult development are deferred in some aspects.[162] While deferrals are, in principle, an appropriate instrument, they could in practice imply delaying patients' access to a potentially promising paediatric medicine. In particular, neonatal studies are very often deferred until experience has been gained with other age groups and this may lead to continuing off-label use for this vulnerable group of patients. The Agency is reviewing internal practices to ensure consistency in its decisions and to avoid lengthy deferrals.

It is also relevant to mention that the Regulation has made it compulsory to publish protocols[163] (which provide details of how a clinical trial is conducted) and the results of paediatric clinical trials.[164] As a result, searchable information is now available about ongoing and completed trials registered in the EU and interventional clinical trials which are included in an agreed PIP. This tool provides crucial information for patients, parents and clinicians on research data and experimental therapies.

The role of rewards

The quantitative impact described above is directly linked to the obligation laid down in the Paediatric Regulation for companies to invest in paediatric research. The reward in this case does not drive paediatric research directly; it is designed as compensation for that obligation, not as an incentive. It is worth noting that the US system does not compensate companies for mandatory paediatric research under the Paediatric Research Equity Act. Financial incentives are provided for voluntary research only on the basis of a priority list which represents a balanced portfolio of therapeutic areas and paediatric needs, without replicating research funded elsewhere.

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159 Section 3.14 of the Agency 10 years report.

160 Idem 199.

161 According to preliminary data received by the Agency.

162 Article 20 of the Paediatric Regulation states that deferrals are to be granted when it is appropriate to conduct studies in adults prior to initiating studies in the paediatric population or when studies in the paediatric population will take longer to conduct than studies in adults.

163 Article 41 of the Paediatric Regulation.

164 https://www.ema.europa.eu/en/human-regulatory/research-development/paediatric-medicines/paediatric-clinical-trials (https://www.clinicaltrialsregister.eu/)

The Regulation specifies that rewards can be claimed only once a PIP has been completed. By 2016, over 40 medicinal products had been granted an SPC extension by national patent offices in one or more Member States. This indicates that the reward system is working. However, the SPC extension is a valuable reward only if it is the last protection to expire, which is very often not the case.[165] Not all companies complying with the obligation introduced by the Paediatric Regulation have been able to receive the reward. In the first 10 years, only about 55% of the products for which a PIP was completed were granted an SPC extension.[166] There are several reasons for this. Not all products covered by the obligation are eligible for an SPC. Moreover, the SPC extension must be requested two years before the certificate expires. Given the length and complexity of the clinical studies to be conducted (most PIPs have a duration of 10 years or more), some companies fail to complete the PIP on time.

However, this deadline is an incentive for companies to speed up the completion of paediatric research, and it ensures that generic competition learns sufficiently in advance about any extension of the protection period that may affect the market launch of generics.

Since the economic value of this reward is directly coupled with the volume of sales within the adult population, however, (the extension of the SPC applies to the whole product, not just to the paediatric indication), the SPC extension is more attractive to pharmaceutical companies with a larger share of the patient group overall. This may encourage companies to prioritise PIPs for products which bring the highest return on investment, not for those with greatest paediatric need. The analysis conducted[167] has shown that the SPC paediatric extension was obtained for all the blockbuster products[168] analysed but one.

While it is not a specific driver, the particular character of the reward system thus affects the Regulation's effectiveness.

The other main reward provided by the Paediatric Regulation, the two-year extension of the market exclusivity period[169] for paediatric orphan products, has been granted in only a few cases. By the end of 2018, eight medicinal products had obtained the two-year additional extension of market exclusivity.

This low number can be explained by the fact that when the paediatric legislation was developed, about 60% of orphan-designated products were off-patent (2003-2004) and

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165 Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe (2018), Chapter 4.1.3.

166 10 years of the EU paediatric regulation, report from the Commission to the European Parliament and the Council (COM/2017/0626, Section 6).

167 Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe (2018), Chapter 5.

168 Products with annual revenues exceeding USD 1 billion.

169 See chapter 3.2.2. of this evaluation.

were thus ineligible for an SPC extension. However, over time this has changed substantially, and in 2013-2016, 95% of the orphan-designated products which had obtained a marketing authorisation were covered by a patent.[170]

It should also be borne in mind that the orphan market exclusivity reward is incompatible with the six-month paediatric extension of the SPC.[171] When an orphan product is still covered by a patent and there is a possibility of requesting an extension of its SPC, this reward may be more financially worthwhile to developers, as it extends protection for all the indications of a product, while the orphan rewards are valid only for indications covered by the orphan designation. This is probably why some companies waived the orphan designation in order to make the product eligible for the SPC extension (there is an example in Chapter 5.2.3. of this SWD).[172]

The Regulation included one instrument to encourage paediatric-specific research for existing products, the PUMA scheme. The impact assessment recognised that the incentives the scheme provides would be weak, despite being considered the best and the most practical. It was considered that only the combination of the PUMA with support for off-label research and an inventory of paediatric needs could make the scheme attractive.

However, despite paediatric research on non-patent-protected substances being financed via the various EU research framework programmes and the inventory of paediatric needs being established, experience with this scheme has been disappointing. By 2018, only six medicines had been authorised. Although the Agency approved more than 20 PIPs with a view to submitting a PUMA, it remains uncertain how many will ever be completed and result in a new product appearing on the market.

Several reasons have influenced the relatively low success of the PUMA scheme. First, trials linked to a PUMA are more difficult to perform: the medicinal products concerned are already available on the market and are often widely used off-label. Consequently, health professionals and patients may not be motivated to engage in studies with older medicines.[173] According to industry representatives,[174] another reason for the limited success may be found in the price agreed by Member States for medicines authorised under the PUMA scheme. Member States seem to recognise little added value in older medicines, even if they include a new age-appropriate formulation or new paediatric indications. This

170 Section 6.2.1. of the Agency's 10 years report.
171 Articles 36 and 37 of the Paediatric Regulation.
172 Chapter 5 (case study Glivec) of the Study on the economic impact of the supplementary protection certificates, pharmaceutical incentives and rewards in Europe (2018).
173 Mukattash TL, Millership JS, Collier PS, McElnay JC. Healthcare professional experiences and attitudes on unlicensed/off-label paediatric prescribing and paediatric clinical trials. Eur J Clin Pharmacol. 67(5):449-461, 2011.
174 Public consultation conducted by the Commission with a view to drawing up the report to the European Parliament and the Council on the 10 years of the Paediatric Regulation (see Annex 2, Synopsis report, for details of the consultation.

means they may not agree on the higher prices – compared with the price of the existing product – necessary to cover the costs incurred through the novel clinical research.

This shows that the commercial success of a PUMA is influenced by complex factors beyond the scope of EU law, which can be hardly addressed at EU level. To some extent, the output is consistent with the impact assessment, which indicated that the scheme might be unlikely to result in sizeable numbers of authorised products.

Nevertheless, surveyed stakeholders (in particular from industry, public authorities and academia) suggest that this tool should be maintained anyway, as it has proven successful in bringing certain products onto the market.[175]

5.1.4 – Impact on unmet needs and the timely availability of products for paediatric medicines

Unmet needs

Thanks to the Regulation, the last 10 years have seen considerable progress in the development of medicines for children in certain therapeutic fields. Rheumatic or infectious diseases are often referred to as prime examples. The significant surge of new treatments for children with rheumatic disorders following the completion of PIPs has transformed a sector that was previously neglected.

At the same time, those positive developments do not follow a strategic plan, but are often linked to developments in adult markets. The starting point for most PIPs is a research and development programme for adults. Progress in a paediatric field is dependent on companies' adult product pipeline. Where the adult needs or market expectations overlap with paediatric needs, children will benefit directly. In contrast, there are many diseases that are biologically different in adults and children, where the disease burden differs, or that only exist in children. With these diseases, the mechanism introduced by the Regulation sometimes struggles to produce results.[176]

This is confirmed by the fact that the therapeutic areas covered by the agreed PIPs do not necessarily correspond to the actual paediatric disease burden, although they cover a wide range of therapeutic areas.[177] WHO data indicate that the disease burden for children from birth to less than 15 years of age is highest for mental and behavioural disorders, neonatal conditions, congenital anomalies, and respiratory diseases. Together, these account for almost 60% of the total disease burden. If we compare the disease burden affecting this group of children in the EU with agreed PIPs/paediatric indications, however, we find that only 3% of PIPs were agreed for mental and behavioural disorders, while the figure for

175 Public consultation on the functioning of the Paediatric regulation conducted by the Commission in 2016
176 This also emerged at the conference held by the Commission in June 2019.
177 Section 3.1 of the Agency 10 years report.

neonatal conditions is just 2%. Instead, the highest proportion of PIPs were agreed for infectious diseases (21%) and malignant diseases (13%), which rank 9th and 10th respectively in the disease burden index (DALYs).[178]

This may result in most developments taking place in areas with limited paediatric unmet needs. For example, many companies have concentrated their research activities on type II diabetes, leading to several new products for adults. This has also resulted in an increase in the number of paediatric products of this type in the pipeline, although type II diabetes is relatively rare in children.[179]

As the legislation was designed to increase the number of medicines studied for children in general, it contained no provisions specifically designed to boost development in particular therapeutic areas. Consequently, the Paediatric Regulation, taken on its own, has limited potential for steering activities towards particular therapeutic areas.[180] Its positive impact and the change in culture it has encouraged are thus most visible in the integration of paediatric development into the overall development of new medicines. It has been less successful with projects aiming to develop remedies for diseases found only in children. The impact assessment had already anticipated the possibility that the Regulation might push development toward the most profitable areas, not towards those with greater unmet needs as far as children are concerned.

A particular area of unmet needs is that of rare diseases in children, bearing in mind that 90% of all rare diseases manifest in childhood.[181]

Looking at the impact of the Orphan Regulation, only about half the 111 orphan products authorised for diseases that start in childhood (56 products) have actually been authorised for use in children. As regards the various therapeutic areas covered by these products, oncological orphan products are somewhat less likely overall to have a paediatric use indication than non-oncological products (34% vs 48% respectively) (Figure 8).[182]

One would expect paediatric indications to be added later, after the completion of a PIP under the Paediatric Regulation. However, by the end of 2016, although 150 PIPs had been agreed for medicinal products which had also received an orphan designation, this resulted in only nine paediatric indications being authorised as orphan medicinal products.[183]

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178 Section 3.2 of the Agency 10 years report.

179 10 years of the EU paediatric regulation, report from the Commission to the European Parliament and the Council (COM(2017) 626, Section 4 (period of reference: 2007-2015).

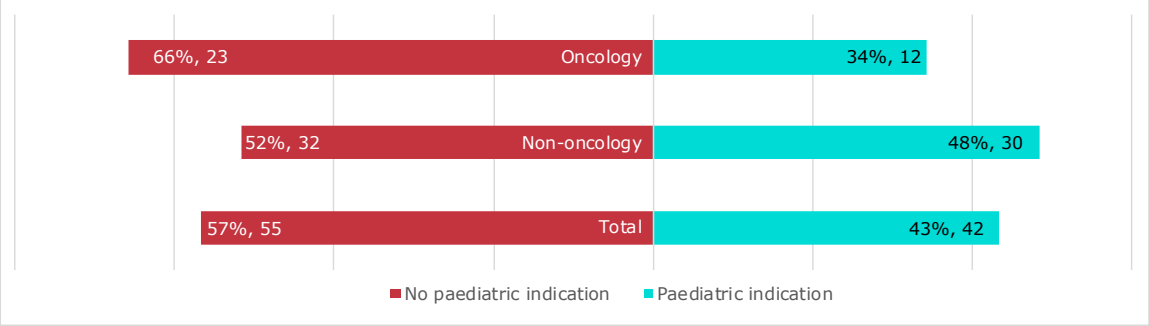
180 For example, the inventory of therapeutic needs developed by the Agency in accordance with Article 43 of the Paediatric Regulation was designed to help developers of medicinal products identify opportunities; this activity is ongoing in the joint Agency-Commission paediatric action plan (action 1).

181 Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database, *European Journal of Human Genetics*, 2019.

182 Section 5.4.5 of the Orphan study report (2019).

183 Section 3.17 of the Agency 10 years report.

Figure 8: Authorised orphan medicines with a paediatric use indication for conditions affecting adults and children, by therapeutic area



Source: Orphan study report (2019).

These figures show that while both the Paediatric and the Orphan Regulations have had a positive impact, they have not been able to solve the problem of the shortage of treatments available for children with rare diseases. This is also confirmed by the concerns raised by 'non-industry' stakeholders.[184]

Furthermore, the SPC extension is incompatible with the orphan market exclusivity. The SPC extension is more attractive to pharmaceutical companies, as it covers a larger patient group overall. This may encourage companies to prioritise products offering the highest potential return on investment, not children suffering from rare diseases.

The focus on conditions that affect adults only, or that affect adults as well as children (as opposed to primarily paediatric conditions), seems to indicate that the two Regulations lack sufficient capacity to incentivise development of specific paediatric medicines. Neither the Orphan Regulation nor the Paediatric Regulation offers specific incentives to promote the successful development of innovative medicines for use exclusively in children.

Availability of and access to paediatric medicines

Issuing a marketing authorisation or adding paediatric information to existing marketing authorisations does not automatically translate into making a product immediately available to paediatric patients in the EU. This may be because of pending reimbursement decisions at national level or doctors' prescription habits. Sometimes, even when a paediatric product is available, off-label use continues for a while, which shows there is some inertia in the system. The majority of respondents taking part in a survey conducted by the Commission in 2017 said the Regulation had led to an increase in the paediatric medicines available at the bedside, and that practitioners were increasingly prescribing approved medicines in accordance with the licensed indication for children. In line with the expectations set out in the impact assessment, while off-label use in children is

[184] Section 9.1.2 of the Orphan study.

decreasing, it is likely to continue to some extent. This is determined by factors independent of the Regulation, such as health professionals' prescription and the reimbursement decisions taken by national health systems.

The launch of a paediatric indication or product on a national market is often linked to the launch of the corresponding adult product. It has been observed that companies often rely on a staggered roll-out of any new products, resulting in delays until the product is finally available throughout the EU. This also indirectly affects the availability of paediatric medicines[185] on the various markets.

This cannot be prevented altogether, even though the Regulation includes some instruments tailored specifically to ensure that paediatric medicines are placed on the market once a PIP is completed and the product has been authorised. First, the reward of a supplementary protection certificate will only be granted once the product has been authorised in all Member States. [186] Second, when a new paediatric indication is authorised for an existing product, the new indication must be placed on the market within two years of the moment of authorisation[187]; and third, if an authorisation holder intends to discontinue the marketing of a paediatric product, they have an obligation to transfer the authorisation to another company or provide access to the relevant data.[188] However, the legal obligations are not sufficiently stringent enough to force companies to place the product on all Member State markets.

5.1.5 – Impact on competitiveness and the research landscape

Neither Regulation was specifically designed to improve the competitiveness of European industry. However, at the time of the proposal for the Orphan Regulation it was thought that companies, especially SMEs, would benefit in terms of job creation and highly qualified jobs.[189] Generally speaking, this would have been a positive secondary effect that could have gone hand in hand with increased research. The impact assessment of the Paediatric Regulation[190] also predicted that it would boost European R&D either directly or indirectly, thereby improving the competitiveness of EU companies vis-à-vis their US competitors.

Although it is not possible to assess the direct impact of the Orphan Regulation on the research environment, or vice versa, it is feasible to assess how the research environment

185 10 years of the EU paediatric regulation, report from the Commission to the European Parliament and the Council (COM(2017) 626, section 3.
186 Article 36(3) of the Paediatric Regulation.
187 Article 33 of the Paediatric Regulation.
188 Article 35 of the Paediatric Regulation.
189 Communication to the Commission about a Draft Proposal for a European Parliament and Council Regulation (EC) on orphan medicinal products and Explanatory Memorandum (p. 6 - impact on firms).
190 https://ec.europa.eu/smart-regulation/impact/ia_carried_out/docs/ia_2004/sec_2004_1144_en.pdf

has changed since 2000. Before the Regulation's introduction, research into orphan drugs was limited, very little expertise was available, and what little there was did not lead to significant progress in research. Since 2000, over €1.4 billion has been made available[191] through the EU's framework programmes for research, technological development and innovation. EU support has improved understanding of the underlying causes of rare diseases, enabled more accurate diagnostics and helped develop new therapies and integrate patient registries and research data.

This ecosystem supports the competiveness of EU industry. In addition, extension of the SPC under the Paediatric Regulation indirectly boosts the competiveness of pharmaceutical companies and provides some guarantee that profits will be redistributed, thus enabling the development of sound R&D infrastructure.[192]

However, it is important to note that decisions on the location of pharmaceutical research and development are driven primarily by factors *other* than a period of protection (such as those granted to incentivise the development of pharmaceuticals) provided in a particular country. Possible relevant factors are the quality of the labour force, tax levels, infrastructure, and research and development subsidies.[193]

5.2 EFFICIENCY

Main findings

The Orphan Regulation has added 210,000-440,000 quality-adjusted life years to the lives of EU patients. This represents a substantial improvement in the quality of life of patients with rare diseases. At the same time, the costs to health systems, mostly paid for by governments, rose by €23 billion between 2000 and 2017. This comes in addition to EU and national public funding invested in research.

The average additional protection offered by the market exclusivity reward was calculated at 3.4 years; 30% of revenues from sales of orphan medicines can be regarded as the value of this reward. The cost-benefit analysis for the pharmaceutical industry associated with the Regulation has been positive.

For the 73% of orphan medicines with an annual turnover below €50 million in the EEA, the market exclusivity reward has helped to increase profitability, without giving the sponsor an unbalanced compensation. However, for the 14% of orphan medicines with an

191 Directorate-General for Research and Innovation (European Commission): 'Rare diseases: A major unmet medical need', November 2017; https://ec.europa.eu/info/publications/rare-diseases_en

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

193 Idem; Section 2.1, Impact on innovation.

annual turnover above €100 million in the EEA, the 10-year market exclusivity may have led to overcompensation, and the incentives may not have been indispensable. The tool to limit market exclusivity in highly profitable cases has proven ineffective.

The Regulation is not entirely efficient. Findings have shown that there are currently 22 orphan medicines on the EU market and that they are authorised for two or more orphan indications. Limited generic competition was shown after expiry of the market exclusivity and/or the protection provided by other pharmaceutical incentives, with a slower price fall for orphans compared to other medicines. Medicines in well-established use and repurposed medicines account for only a small share of the orphan drugs that have reached the EU market.

Taking into account both the direct and the indirect induced effects, the cost-efficiency of the *Paediatric* Regulation has had a positive cost-benefit ratio for both pharmaceuticals companies and society in general. However, not all companies have reaped direct rewards from their investment in research, and costs to society have been created that are linked to monopoly rents.

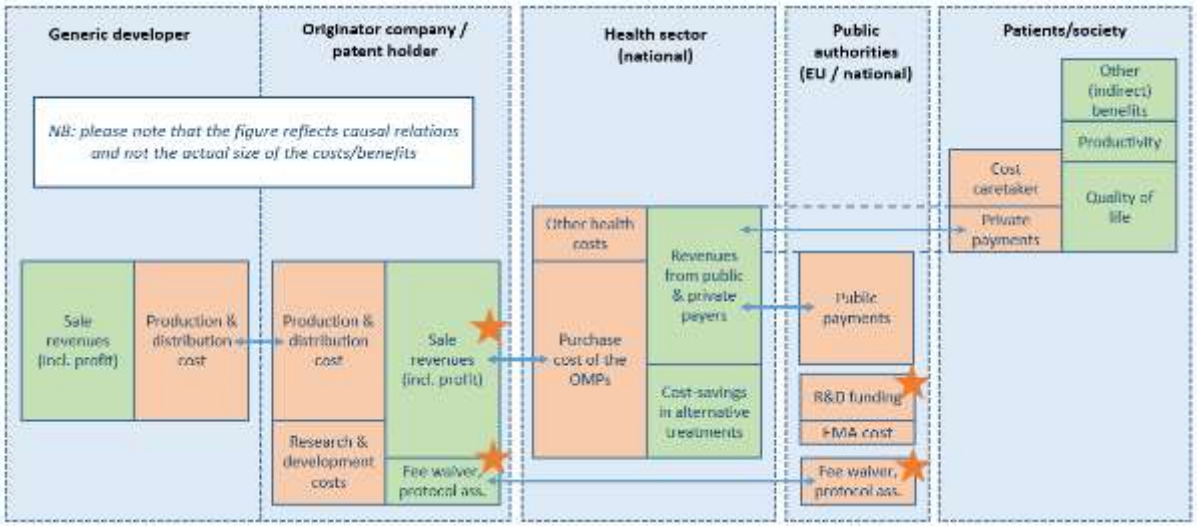
Nevertheless, developers still perceive this legislation as burdensome and the main reward provided and the extension of the SPC is reported to be inefficient and complex.

5.2.1 How costs and benefits of the Orphan Regulation have been distributed

The changes brought about by the Orphan Regulation (in terms of the development of new orphan medicines, a faster introduction to the EU market and a wider accessibility to such products[194]) have resulted in both extra costs and benefits for the following stakeholder groups: the pharmaceutical industry, the health sector, public authorities and patients, and society in general.

Figure 9: Overview cost (red) and benefits (green) for various stakeholders

[194] For more details, see Section 1.4.2. of Annex 3.



Source: Orphan study report (2019) (Note: the schematic reflects only causal relations but not the actual size of the costs/benefits; the orange stars refer to the four 'rewards' the Orphan Regulation introduced (i.e. market exclusivity, protocol assistance, fee waivers and aid for research).

- *Pharmaceutical industry*[195]

With few exceptions, companies were unwilling to share an estimate of the average total R&D costs per product.[196] The costs of developing an orphan medicinal product have been estimated to range from €479 million to €725 million, the average being €602 million. This estimate does not take account of well-established use and repurposed medicines (for which R&D costs are much lower). The estimated R&D costs for an orphan medicine appear to be lower than those for a non-orphan (around 27%).[197]

The analysis took account of the fact that R&D costs can potentially be spread over worldwide sales; not all of the R&D investments made by the companies concerned can be assigned to the EU market. In the absence of clear data on the share of sales in the EU compared to worldwide sales of medicines for rare diseases, several assumptions were made. They led to the conclusion that the Orphan Regulation has resulted in an increase of €11 billion in R&D expenditure on orphan medicines over 2000-2017.[198]

195 There are two types of sponsors in the pharmaceutical industry: developers of innovative medicines ('originators') and developers of generic medicines. While both originators and developers of generic medicines need to cover the costs of manufacturing, marketing and distribution of orphan medicines in the EU, it is the originators that cover R&D costs. These costs are limited for developers of generic medicines.

196 Section 8.2.2. of the Orphan study report (2019).

197 Section 8.2.2. of the Orphan study report (2019).

198 The sum of €11 billion corresponds to the rounded extra R&D costs of 21 extra products attributed to the EU Regulation. See also Section 2.1. of Annex 3.

To assess the costs of manufacturing, marketing and distribution of orphan medicines, the results of the analysis of the economic value of the market protections were taken into account. Analysis based on a sample of four orphan medicines where generic entry was observed[199] shows that 30% of revenues from sales of orphan medicines can be regarded as the value of the market exclusivity reward, while, on average, 70% of revenues[200] reflect the turnover level that would apply under competitive market conditions (i.e. following generic entry or in cases where generics could potentially enter the market).

Based on the extra sales of €19.1 billion, the extra cost of selling medicines in 2000-2017 was calculated at €12.04 billion (after correction for a 'competitive profit margin'). This margin was assumed to be 10%[201] (and added to the cost-benefit as a benefit) of the 'net' turnover (i.e. turnover minus the orphan exclusivity share).[202]

The most obvious 'benefit' from the Orphan Regulation to developers of orphan medicines is that, should they successfully bring a product to market, they will be able to generate additional sales in the EU/EEA. Thanks to the Orphan Regulation, orphan medicines enter the EU/EEA market faster and are more widely available (higher volumes) within the EU/EEA. All effects taken together have resulted in increased sales of orphan medicines in the EU market of an estimated value of €19.11 billion[203] between 2000 and 2017.

The additional 3.4 years of protection period resulting from the market exclusivity are estimated to bring an extra R&D compensation (margin of 30% for an additional number of years) of €4.59 billion. In addition, the fee waiver and protocol assistance rewards under the Orphan Regulation during 2000-2017 are estimated to have a value of €0.16 billion.

Table 3: Industry costs and benefits (originators) that can be ascribed to the Orphan Regulation, 2000-2017 (discounted value 2018, prices 2018, in billions of euros)[204]

Effect	Costs	Benefits
R&D costs associated with the additional orphan medicines developed (EU part)[a]	-/- €11.0b	
Sales revenues of additional orphan medicines in EU		€19.11b
Costs of manufacturing, marketing, distribution and applicable taxes relating to additional sales of orphan medicines in EU	-/- €12,04b	
Extra R&D compensation due to market exclusivity reward		€4.59b

199 Section 8.3.2. of the Orphan study report (2019).

200 This 70% is derived from the assumption of a 30% 'market rent' due to the orphan exclusivity.

201 See, for instance, Hill et al., 2018, that aimed to 'estimate the generic price that can be achieved if profit margins are competitive'. Although more specific profit margins are likely applicable to this specific market setting (low volume and low number of competitors), these were not readily retrievable from the literature.

202 A margin of 7% (10% of 70%) is the amount remaining (after subtracting the 30% exclusivity reward) as a 'competitive profit margin' (a margin that would apply, for instance, where there is generic market competition). 37% x 19.11b = 7.07 billion as a net benefit of additional orphan medicines in the EU. This implies that the cost of selling these extra orphans is 12.04b (19.11b - 7.07 b).

203 Almost 45% of this is attributable to sales from newly developed orphan medicines, another 44% is due to faster access to the EU/EEA market for the other 110 orphan medicines, and 11% can be attributed to the wider spread of medicines.

204 Section 8.2.2. of the Orphan study report (2019).

Cost saving due to protocol assistance and fee waivers		€0.16b
Total	-/- €23,04b	€23.86b
NET BENEFIT	+€0,82b	
Range Net Benefits (minimum – maximum)	-/- €11b to +€11b	

Source: DG SANTE, on the basis of the Orphan Study (2019)

It is hard to assess the total net benefit to industry in the overall calculation of costs and benefits, given a lack of data on R&D costs, the costs of manufacturing, marketing and distribution, and profit margins. Applying some assumptions enables us to establish the net benefit at about €0.82 billion (over 2000-2017). However, there is a margin of uncertainty around this estimate of net benefit.

First, the costs of research and development are based on figures found in the literature. They may thus be underestimates or overestimates. The full costs of developing the 21 orphan medicines in this analysis have only been compared to revenues generated in the reference period (2000-2017). Many of these products have only been on the market for a relatively short time, and they can reasonably be expected to continue generating revenues and profits for the industry long after 2017. Moreover, revenues from other jurisdictions (such as the US and Japan) were not taken into account when attributing R&D costs to the Regulation, although the global market for orphan medicines is very much dependent on the US.[205] It may thus be assumed that the balance for industry is more positive than a benefit of €0.82 billion over 2000-2017.

- *Health sector*

The health sector, comprising all medical services needed to treat patients suffering from rare diseases[206], bears the costs of treatment with orphan medicines. These costs consist of the extra use of orphan medicines resulting from the Orphan Regulation and the additional healthcare costs (additional costs of treatment with orphan medicines, minus savings on costs of alternative treatments). As it was not possible to assess the additional healthcare costs, given the limited information provided in the available HTA reports, the extra costs to the healthcare system have been assumed to be equal to the extra revenues realised by industry (sales revenues of €19.1 billion and additional R&D compensation due to the market exclusivity reward of €4.6 billion), making a total of €23.7 billion.

These costs are financed from a combination of public sources (taxation or compulsory health insurance premiums) and private ones (patients' own contributions in the form of out-of-pocket expenses and voluntary health insurance premiums). For the purpose of this

[205] 70% of global revenues from orphan medicines come from the US alone (Orphan Drug Report 2019, EvaluatePharma).

[206] Section 8.2.1. of the Orphan study report (2019).

cost-benefit analysis, it has been assumed that 97% (€23.0 billion) of healthcare costs were covered by public funding, while 3% (€0.7 billion) were privately financed.[207]

Table 4: Costs and benefits due to the EU Orphan Regulation for the health sector, 2000-2017 (discounted value 2018, prices 2018, billions of euros)[208]

Effect	Costs	Benefits
Extra costs due to treatment with orphan medicines	-/- €23.7b	
Additional extra costs due to new treatments (e.g. clinical costs)	NDA[209]	
Savings in costs of alternative treatment		NDA
Public and private financing		€23.7b
TOTAL	-/-€23.7b	€23.7b
NET BENEFIT		€0.0b

Source: Orphan Study (2019)

- *Public authorities*

In addition to financing public healthcare, public authorities incur *additional* administrative costs associated with implementing the Orphan Regulation. These additional costs are related to:

- the functioning of the Agency and committees, such as COMP (estimated at €0.02 billion);
- research subsidies provided by the EU and various national governments (estimated at €1.1 billion);
- fee waiver and protocol assistance[210] (estimated at €0.2 billion) as an integral part of the support provided by the Agency.[211]

A large proportion of the additional healthcare costs is reimbursed from collective sources (government budgets, collective health insurance systems, or other sources).

Although healthcare systems across the Member States are organised and funded in different ways, orphan medicines are generally financed from public sources. Survey respondents from national public authorities indicated that, in most Member States (17 out of 20, 85%), the reimbursement mechanism for orphan medicines is the same as for non-orphan products. Orphan medicines are financed by a national health service in the majority of cases (15 out of 20, 75%). In a minority of cases (6 out of 20, 30%), orphan

207 See Section 2.4. in Annex 3 for assumptions.
208 Section 8.2.3. of the Orphan study report (2019).
209 No data available.
210 The Agency's fee system was evaluated in 2019. The outcome of this evaluation shows that the current fee system is generally efficient and effective, including in funding some non-fee-generating and uncompensated activities, as well as reductions and fee waivers. See: https://ec.europa.eu/health/human-use/legal-framework/ema_fees_en
211 The costs of this assistance, incurred by the Agency, are fully financed by the EU.

medicines are also partly financed by a health insurance system. For six reporting Member States (30%), out-of-pocket payments are reported.[212]

Table 5: Costs (attributable to the Orphan Regulation) to national governments and the EU, 2000-2017 (discounted value 2018, prices 2018, billions of euros)[213]

Effect	Costs	Benefits
Administrative costs to the EMA and national authorities	-/- €0.02b	
Aid for research	-/- €1.1b	
Fee waivers, protocol assistance	-/- €0.2b	
Healthcare financing	-/- €23.0b	
TOTAL	-/- €24.3b	€0.0b

Source: Orphan Study (2019)

Costs to public authorities attributable to the Orphan Regulation have been estimated at €24.3 billion. They included the estimated costs to healthcare financing of orphan medicines and the additional administrative costs set out in Table 4 (putative benefits to public authorities have not been identified and included).[214]

- *Patients and society*

This stakeholder group is affected by rare diseases either directly, as patients, or indirectly (e.g. as carers or relatives).

It was assumed in the analysis that in the EU, 97% of all healthcare *costs* arising from orphan medicines and associated treatments are financed from public sources. At €0.7 billion, the private contribution to healthcare costs was limited.[215]

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, whether professional or informal, outside the healthcare system; 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.[216]

In fact, the societal cost perspective adopted in the present analysis does not take account of productivity losses in society avoided thanks to the Orphan Regulation. Moreover, the costs and benefits are based on an assessment of the 2000-2017 period, which was the Regulation's start-up phase. In the longer run, it is to be expected that more generics and biosimilars will enter the market as products' orphan status expires, resulting in lower costs

[212] See Section 1.4.2. of Annex 3 for detailed calculations.
[213] See Section 2 of Annex 3 for detailed calculations.
[214] See Section 2.3. of Annex 3 for detailed calculations.
[215] See Section 2.4. of Annex 3 for detailed calculations.
[216] The calculated societal cost-effectiveness (outcome-efficiency expressed in terms of euros per health effect gained) of the Orphan Regulation is not out of line with the upper cost-effectiveness values commonly observed in health economic evaluations of new technologies for EU healthcare systems.

and/or greater availability of treatment for patients. All this means that the calculated societal cost-effectiveness of the Orphan Regulation presented here is based on a comparatively *conservative* assessment; it takes account of extra costs, but not of the long-term savings that may be expected in future.

Health *benefits* reflect the improvement in patients' quality of life attributable to treatment with orphan medicines. They can be expressed and measured in the number of QALYs[217] that patients gain per incremental cost.[218] The level of health benefits was assessed using information on the incremental cost-effectiveness ratio (ICER)[219] from HTA reports.[220] The Orphan Regulation's cost-effectiveness for society can be considered acceptable when compared to ICER thresholds in use internationally.[221]

Based on a multiplication of the calculated ICERs (range €54,000 to €110,000) and the estimated extra healthcare costs presented in Table 4 (Costs and benefits due to the EU Orphan Regulation for the healthcare sector, 2000-2017), an estimated 210,000 to 440,000 QALYs were gained thanks to the Regulation (2000-2017).[222] The wider *economic* benefits could not be established at the level of the EU Orphan Regulation. However, they are likely to be a positive value, given that rare diseases are often very disabling and represent a heavy burden on society.

Table 6: Costs and benefits to patients arising from the Orphan Regulation, 2000-2017 (discounted value in 2018; prices 2018, billions of euros)[223]

Effect	Costs	Benefits
Private contribution to healthcare costs	-/- €0.7b	
Change in non-health costs of disease	NDA	
Health benefits		210,000 – 440,000 QALYs
TOTAL	-/- €0.7b	

Source: Orphan Study (2019)

217 QALYs (quality-adjusted life years) are 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 quality of life.

218 Direct impacts on healthcare costs are typically taken into account in health technology assessments (HTAs). The extra costs to the healthcare system had to be assumed to be equal to the extra revenues accruing to industry because only a few HTA reports contain all the relevant elements around cost of treatment with orphan medicine and cost savings for alternative (comparator) treatment, QALYs and ICERs.

219 ICER is a measure of the 'value for money' a medicine offers in comparison to other treatments. ICERs were available for 32 orphan medicines. 24 ICERs relate to orphan medicines that have not been withdrawn from the market and for which sales were recorded in the EU.

220 ICERs were available for 32 orphan medicines, 24 of which were orphan medicines that have not been withdrawn from the market and for which sales were recorded in the EU.

221 See, for instance, the threshold of €80,000 per QALY in the Netherlands. (https://kce.fgov.be/sites/default/files/atoms/files/d20081027396.pdf).

222 See Section 2.4 of Annex 3 for detailed calculations.

223 Section 8.2.5. of the Orphan study report (2019).

To conclude, while the above estimates of costs and benefits to different groups of stakeholders are informative, they cannot directly answer the question of whether the balance of costs and benefits is proportionate or 'fair'. Most costs 'trickled down' to national governments, which has caused frictions, political and otherwise, in recent years. Although no firm conclusions can be drawn as to whether the extra revenues resulting from the Orphan Regulation outweigh the additional R&D investments, it is likely that a more positive value for industry would have been obtained if revenues from non-EU jurisdictions and post-2017 profits had been taken into account in the analysis.[224]

Affordability

The Regulation's efficiency is certainly influenced by pricing and reimbursement considerations, which are linked to affordability. However, these lie beyond the EU's remit.[225]

The final judgement on the fairness of the balance of costs and benefits is a qualitative assessment based on the value placed on health gains and a reasonable profit margin. Member states applying cost-effectiveness analysis to inform reimbursement decisions for new medicinal products often will do so using QALY. For orphan products specifically an average cost of €54,000 per QALY can be observed based on available cost-effectiveness analyses and market shares (weights for the average).

Nonetheless, even medicines that are assessed as exceeding such threshold values are sometimes reimbursed under pressure by advocacy groups and public opinion. This indicates that within societies there is substantial willingness to pay for medicines to treat rare diseases, sometimes at a very high cost. At the same time, 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.

The important question, then, is whether the prices charged for medicines to which additional exclusivity rights are granted are reasonable in relation to the developer's investments, especially in cases where development was supported by public research funding.

5.2.2. Level of compensation for orphan medicinal products

The main purpose of market exclusivity was to extend the time during which the marketing authorisation holder could charge a 'monopoly rent' to recover the investment made.[226] The analysis evaluated whether market exclusivity offers sufficient compensation to

[224] See limitations in Chapter 4.2. of this SWD.

[225] As already described in Chapter 2 (Background to the intervention) of this SWD.

[226] A monopoly rent refers to a situation in which a monopoly producer lacks competition and can thus sell its goods and services at a price above (and sometimes far above) the otherwise competitive market price (at the expense of consumers and payers).

encourage investment in developing orphan medicines. This assessment includes a comparison of the market characteristics of orphan and non-orphan medicines, a calculation of the economic value of market exclusivity, and the impact of competition on the compensation provided.

The analysis of turnover of non-orphan, orphan and 'orphan-like' medicines in the EU/EEA[227] showed that in 86% of cases turnover levels for orphan medicines were below €100 million per year, with most having a turnover below €50 million. Similar turnover levels could be observed for orphan medicines introduced before the legislation came in (the 'orphan-likes'). Only for a subset of orphan products (14%) or orphan-likes (17%) was the annual turnover estimated to exceed €100 million. By contrast, the average turnover of non-orphan products introduced after 2000 was estimated to be almost 50% higher than that of orphans.[228]

Table 7: Distribution of average annual turnover (2008-2016) for various types of products in the EU, by turnover class (millions of euros per year)

	<€10 m	€10-50 m	€50-100 m	>€100 m	Average turnover
Orphan-likes (N=82)	60%	18%	4%	17%	€ 79 m
Orphan medicines (N=105)	48%	25%	13%	14%	€ 56 m
Newly introduced non-orphan medicines (branded products) (N=1,071)	50%	20%	10%	20%	€ 83 m

Source: Orphan Study (2019)

On average, evidence suggested that market exclusivity extends by 3.4 years the period for which authorised orphan medicines are protected from generic competition. Furthermore, with a sample of 16 orphan medicines it was possible to determine a new equilibrium price for four products,[229] based on the price realised by generic competitors. The economic value of market exclusivity reward for this limited sample of products averaged 30% of total turnover.[230]

For most orphan products, in particular those with an annual turnover below €50 million and average R&D costs, it was estimated that the market exclusivity reward helped to increase profitability, without giving the sponsor an unbalanced or unfair compensation. However, 14% of orphans had high sales turnovers in the EU (above €100 million) and

227 See Section 6.1.1. of the Orphan study report (2019).

228 As already stated in Chapter 4.2, the following limitations to the IQVIA database applied: data on revenues and volume data only covered 2008–2017 for most EEA countries (excluding Cyprus, Malta, Denmark, Iceland and Liechtenstein); the IQVIA data did not include revenue and volume data in non-EU jurisdictions (like the US); revenues were based on list prices (and not on net prices).

229 For more details, see Section 1.4. of Annex 3.

230 For detailed calculations, see Section 2.1. of Annex 3.

would not need a 10-year market exclusivity reward to be commercially viable, unless R&D costs were much higher than the average estimates (see Chapter 5.2.1).

However, low turnovers do not necessarily mean that the return on investment in orphan medicines is 'insufficient', as this depends on the specific situation. It is important to take into account development costs (which are mostly unknown) and the issue of whether there is generic competition after expiry of any protection for a given product.[231]

5.2.3. Cost reduction and inefficiencies associated with the Orphan Regulation

The following possibilities for cost reduction have been identified.

First, cost savings could be made if the market was able to switch rapidly to generic medicinal products after the expiry of market exclusivity and/or protection of other pharmaceutical incentives. In the analysis of 16 orphan medicines[232], generic competition was observed only for three orphan products; the price decrease at individual level was not known.

Possible reasons could be that other protections are still in effect, either in the EU (patents, SPCs, data exclusivity and market protection) or in the US. Another reason could be the prospect of too small a return on investment.

Also, a substantial share of authorised orphan medicines are biological molecules, so competition depends on developing biosimilars. All surveyed developers of biosimilars indicated[233] that the complexity of development and/or manufacturing influences decisions on whether and when to develop a biosimilar version of an orphan medicine. In addition, matching the quality of the reference orphan medicine can be challenging, as manufacturers control the release of commercial supplies.

As market exclusivity and/or the protection of other pharmaceutical incentives of more authorised orphan medicinal products are set to expire in the next few years, we are likely to see increased generic entry in the near future. Recent data shows that the overall price fall after generic uptake is 50% for medicinal products in general.[234] For orphan medicines, the literature suggests that prices have so far tended to fall more slowly on generic entry.[235] Potential cost reductions could also be achieved by reconsidering those of the Orphan Regulation's provisions that are designed to limit excessive profits and allow faster entry of similar medicines onto the market, by reducing market exclusivity after five years.

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231 While the expectation of low returns on investment can indeed drive market failure, it is by no means the sole reason. Insufficient basic research, lack of scientific leads for product development, and the complexity of the clinical trials of medicines for rare diseases all play an important part as well.

232 See Section 1.4. of Annex 3.

233 Section 8.4.3. of the Orphan study report (2019).

234 Section 2.3 of the Study on the economic impact of the supplementary protection certificates, pharmaceutical incentives and rewards in Europe (2018).

235 Section 8.3.4. of the Orphan study report (2019).

Under the existing rules, orphan status cannot be challenged on the grounds of product profitability if such status was not sought on the basis of the 'insufficient return on investment' criterion. As applications for orphan designations have so far, in all cases but one, been based on the 'prevalence' criterion, it has been practically impossible to trigger a reduction of the market exclusivity period for any orphan product.

Potential inefficiencies and undesirable consequences may also arise from 'indication stacking', well-established use, and repurposing, as further explained below.

'Indication stacking'

There are currently 22 orphan products authorised for two or more orphan indications on the EU market. These indications refer to distinct orphan conditions, and each entitles the product in question to a period of market exclusivity. These periods may run in parallel, with their own start and finish dates. Similar trends can be observed in the US: of 251 orphan medicinal products authorised between 2008 and 2017, 15.9% had two orphan indications, while 7% were approved to treat *three or more* orphan indications.[236]

While these products have served patients in need and public health, thanks to the extension of the areas in which they can be used, there are also *negative* aspects. If a product receives an authorisation for an additional indication or indications, it is assigned a *new* period of exclusivity for that specific indication. However, it is often unclear whether such a period is really necessary to recover the additional costs of R&D.

While overlapping or consecutive periods of market exclusivity can delay generic entry and may block the development of generic orphan medicines, they cannot prevent generic entry altogether, as each exclusivity period is tied to a specific orphan indication. A manufacturer willing to produce and market a generic version of an orphan medicine once the first market exclusivity period has expired is entitled to do so.

The discussion on *whether* and *how* to reward the development of these 'follow-on' products, after the orphan medicine is authorised for the first indication, often goes hand-in-hand with concerns about a practice known as 'salami slicing'. This phenomenon refers to splitting certain common diseases into many 'artificial' subsets. Each of these subsets could then be considered a rare disease (such as certain forms of cancer).[237] Under the EU Regulation it is possible to obtain orphan designations for subsets of common diseases (although only subject to stringent conditions). At the same time, advances in personalised medicine, may add another layer of complexity to the current regulatory framework. Such developments may hold great potential for optimal tailoring of treatments to diseases and

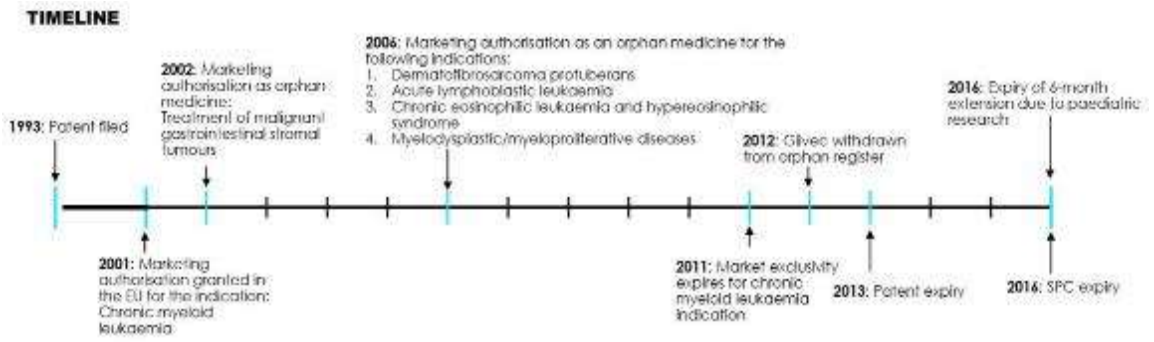
[236] US Government Accountability Office Report on orphan drugs, November 2018, p. 23.

[237] The prevalence of a condition would consequently be based on the sub-type and sub-population. The aim of this is to obtain the incentives associated with the Regulation through these new subgroups.

patients. However they should not lead to unnecessary multiplications of rare diseases out of common diseases, to gain market exclusivity periods.

The number of products authorised for multiple orphan indications in the EU is relatively small, and, in most of those cases the periods of market exclusivity for each indication overlap to a very significant extent. Various stakeholders[238] suggest that reducing the 10-year market exclusivity period for each subsequent indication is a possible way to limit inefficiencies and potential overcompensation. When considering eligibility for orphan designation, it might thus be preferable to consider cumulative prevalence for all the indications covered by the product, rather than the prevalence of each individual indication.

Figure 10: Example of a product with multiple therapeutic indications benefiting from a number of pharmaceutical incentives (including orphan and paediatric incentives)



This figure illustrates how different pharmaceutical incentives are granted at different stages of a pharmaceutical product's life cycle. The case study of Glivec,[239] an anti-cancer medicine authorised for a range of orphan indications, may be instructive here.

A PIP was also conducted, and the company subsequently *deregistered* Glivec as an orphan medicinal product, which provided the opening to file for an SPC extension and thus to benefit from six months of additional protection under the SPC system. At the same time, the same company still had a similar product (Tasigna) with therapeutic applications that overlapped with those of Glivec. (The company had maintained orphan market exclusivity for this product, which enabled it to benefit from both the orphan and the paediatric system.)[240]

238 Section 8.4.1. of the Orphan study report (2019).

239 Data taken from Chapter 5.3 of the Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe (2018).

240 Chapters 5.4 and 7 of the Study on the effects of supplementary protection mechanisms for pharmaceutical products (Technopolis, 2018).

There are currently four *generic* versions of Glivec on the market. All were granted a marketing authorisation in 2013.

Well-established use and repurposing

19% of orphan medicinal products[241] have reached the EU market under these criteria. By way of a comparison, about 38% of orphan medicinal products newly authorised in the US between 2008 and 2017 were authorised for a new indication of a medicinal product previously approved to treat a rare or non-rare disease.[242]

Products authorised through this 'route' have attracted substantial scrutiny because of recent cases in which producers substantially increased the price of a newly-authorised medicine that was already available to patients, at a far lower price, as a magistral formula or in the form of hospital preparations.

Chenodeoxycholic acid (CDCA) for the treatment of a rare genetic disease, Cerebrotendinous Xanthomatosis (CTX). CDCA was originally developed in 1976 as a treatment for gallstones. However, it had already been used since the late 1970s as an off-label treatment for CTX, most recently as Xenbilox, marketed by Sigma Tau. Since the medicine had not previously been authorised for the treatment of CTX, and as it met the designation criteria, an orphan designation was granted to Leadiant (Sigma Tau's new name). Not long after this, the company raised the price of the medicine around 500-fold, causing a public outcry, since the investment the company had to make to 'develop' the product as an orphan medicine had been minimal: CDCA had already been shown to be safe and effective and it was registered on the basis of a literature review and two retrospective cohort studies.

These price increases often bear no relation to actual R&D costs. Market exclusivity is the main factor enabling them to engage in monopolistic price setting.

The fact that the current regulatory framework for the Orphan Regulation contains no provisions to safeguard the affordability and accessibility of orphan medicines, even when no significant R&D investments have been made, may be regarded as a significant inefficiency. However, the absence of data on the costs of development for such products makes it difficult to objectively estimate what would constitute an appropriate reward.

In 2016, a Commission notice[243] was issued with the aim of limiting inappropriate use of the Orphan Regulation, such as may occur when sponsors apply for orphan designations on products that have long been in use in the medical community. However, it has proven problematic to apply, as the information available in scientific literature on the use of

[241] Data up to 2018 (Section 5.5 of the Orphan study report (2019)).
[242] US Government Accountability Office Report on orphan drugs, November 2018, p. 24.
[243] Commission notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products, C/2016/7253; OJ C 424, 18.11.2016, pp. 3–9.

hospital preparations is often very limited. Although sponsors are expected to do due diligence and provide all available evidence from their own studies and literature, the COMP has limited means at its disposal to verify whether the information is complete. A similar trend was observed in the US, where it was noted that the FDA does not always ensure that all information is consistently recorded in its review templates and evaluated when making designation determinations.[244]

5.2.4. How the costs and benefits of the Paediatric Regulation have been distributed

The costs and benefits of the Paediatric Regulation have been quantified for the relevant stakeholder groups and a cost-benefit analysis has been undertaken.

- *Pharmaceutical industry*

The 2016 economic study estimated the total annual costs incurred by industry in connection with the Paediatric Regulation at €2,106 million, of which €82 million are administrative costs, while the rest is associated with paediatric R&D (mostly concerning clinical trials agreed in PIPs).[245]

Average costs incurred per PIP are estimated at €19.6 million. Of these, 4% (€728,000) are administrative costs arising from the application for a PIP and possible modifications, while 96% (€18.9 million) are R&D costs.[246] These estimated costs are normally incurred over several years, as the average duration of a PIP is between 5 and 10 years (though some are expected to last over 20 years).[247] However, the costs incurred for an individual PIP vary significantly. They depend on such matters as the number of clinical studies included in the PIP, the number of subjects involved in the trials, the duration of a PIP, the therapeutic area, the scale of cooperation with clinical and research networks, and the number of modifications of the PIP that are required. Table 7 shows the estimated average costs of each stage of a PIP, as well as the percentage of PIPs that incur such costs.[248] Details of the calculations concerning the cost of compliance with the Paediatric Regulation are given in Annex 3, in section 1 of the paediatric part.

Table 7: Estimated costs of a PIP, broken down into stages, and the percentage of PIPs that incur such costs (based on data for completed phases only, 2008-2015), in millions of euros)

244 US Government Accountability Office Report on orphan drugs, November 2018, p. 34.

245 Final Report of the Study on the economic impact of the Paediatric Regulation, including its rewards and incentives (December 2016); Section 2.2.

246 R&D costs include the costs of in-vitro studies and animal studies conducted during the development of a paediatric formulation, clinical trials, and other R&D costs.

247 Final Report of the Study on the economic impact of the Paediatric Regulation, including its rewards and incentives – December 2016, Section 2.2.4.4.

248 Final Report of the Study on the economic impact of the Paediatric Regulation, including its rewards and incentives – December 2016, Section 2.2.

Stage	Average	% of PIPs incurring costs	% of PIPs incurring costs if PIP is discontinued
Preparation of the initial PIP application	€0.4	100	100
Annual reporting and further PIP modifications	€0.1	55	29
Other administrative costs	€0.2	42	21
In-vitro studies and animal studies	€0.8	40	36
Development of a paediatric formulation	€1.6	47	29
Phase II paediatric clinical trials	€7.3	48	21
Phase III paediatric clinical trials	€15.7	72	36
Other R&D costs[249]	€14.4	44	21

Source: Study on the economic impact of the Paediatric Regulation (2016)

The system underpinning the Regulation is built on the assumption that products covered by the PIP requirement should be eligible for a reward, once paediatric development is completed, to balance the investments made by industry. However, this is not always the case. In fact, when an adult development programme stops, the PIP is often discontinued as well. The administrative and R&D costs of discontinued PIPs are estimated at €144 million per year.

To calculate the economic value of the SPC reward, the analysis focused on eight products which (1) received an SPC extension between 2007 and 2012, and (2) lost their exclusivity before the third quarter of 2014. The results were then extrapolated to four further products. The sample size was quite small, as only a fraction of products with completed PIPs have lost protection so far, so the data on how this affects revenues are limited. Moreover, the figures for those products may need to be interpreted with some caution, as companies may, in the early years, have prioritised products predicted to earn the highest return on investment through the SPC extension.

There are significant differences between products and countries, most likely linked to the competitiveness of the particular therapeutic market and/or national policies to encourage generic substitution. Consequently the economic value of the SPC extension varies considerably as a percentage of total revenue (between 10% and 93%, averaging 56.6%). Overall, the adjusted economic value of the SPC reward for the eight products concerned amounts to €926 million, with revenues especially geared towards some blockbuster products included in the sample size.[250] Details of the calculations underpinning the analysis of the economic value of rewards and/or incentives are provided in Annex 3 (section 2 of the paediatric part).

[249] Other R&D costs are incurred through activities ranging from, for example, preparing study outlines; medical writing for a clinical plan, including data and database management; coordination activities and transaction costs; and conducting non –interventional studies.

[250] Study on the economic impact of the Paediatric Regulation, including its rewards and incentives – Final Report, December 2016; Section 3.2.6.

The impact assessment conducted on the proposal for a Paediatric Regulation estimated that the value of a six-month extension of the SPC would offset the costs incurred by companies through mandatory paediatric testing. In certain cases, companies would make profits as a result. If an SPC extension is granted, it usually covers the costs incurred through the PIP (€926 million in revenue for 12 products, against average costs of €19.6 million per PIP).

However, it is important to note that up to 2016 only 55% of completed PIPs benefited from a reward. While it is expected that over time the proportion of products that benefit from this reward will increase, as companies start to plan their paediatric research better and earlier, it is unlikely that the success rate will ever reach 100%. This eventuality was not considered in the impact assessment.

In turn, it was not possible to estimate the economic value of the orphan reward and the PUMA. As regards the orphan reward, this was because only a limited number of products have benefited from it, most of which are still under protection. As for the PUMA, the 2016 economic study concluded that, in line with one of the possible scenarios laid down in the impact assessment, this reward does not seem to offer meaningful market exclusivity because the product can, in any case, be subject to off-label use of generics.[251] Furthermore, the fact that the new indication needs to be developed exclusively for children in order to be eligible for the PUMA often makes it too costly and complex, especially for SMEs. All of these points make projections of the commercial value of the product and the possible return on investment less predictable for companies.

Nevertheless, the risk-benefit analysis, detailed in Annex 3 (paediatric part, section 4.7), shows how the economic spill-over effects resulting from private R&D investments, which would not have happened without the Regulation, lead to the creation of more jobs and the promotion of innovation across sectors. A €2 billion investment in R&D associated with PIPs produces a €3.2 billion return in both the pharmaceuticals sector and in other sectors of the economy over 10 years.[252]

- *Regulatory authorities*

The Paediatric Regulation says that the EU budget's contribution to the Agency covers the work of the Agency and its PDCO committee. It is also intended to support the Agency's

[251] In many cases, healthcare professionals prescribe cheaper generic products off-label, in preference to the newly-authorised paediatric indication. In addition, national healthcare systems may be reluctant to reimburse the PUMA-rewarded product when cheaper alternatives are available.

[252] Administrative costs are not included in this calculation. They can be estimated at €78 million/year for all PIPs. Even if such figures were included, the cost-benefit calculation for industry would thus remain positive.

activities associated with the publication of paediatric clinical trials and the European network.[253]

It should be noted that part of the costs associated with PIP procedures conducted by the Agency are borne by national competent authorities contributing to the Agency's scientific work, which are not remunerated. On the basis of unpublished data on the costs of paediatric-related activities collected for the Commission report on the evaluation of the European Medicines Agency's fee system[254], the annual costs of NCAs for PIP assessment were estimated at €0.6 million, those of waiver assessments at €90,000 and those of compliance checks at about €50,000 per year.[255]

The impact assessment for the Paediatric Regulation estimated increased annual costs to regulators at €5 million, and in particular for EMA. This estimate seems to be correct, as the calculated average cost-base fee for industry for paediatrics was estimated at €4.8 million/year in the fee study.[256]

- *Society and patients*

The cost-benefit analysis under the Paediatric Regulation takes account of the benefits to society and children's health resulting from the Regulation's application. These benefits are: the switch from off-label to more on-label use of medicines, better treatment for children, fewer adverse drug reactions, shorter periods in hospital, better quality of life for children, increased school attendance, and less time spent by carers. The spill-over effects of industry's research investments are also taken into account. Details of the cost-benefit model and related calculations are given in Annex 3, sections 3 and 4 of the paediatric part.

The costs to society arise from the extra monopoly rent accruing to the company through the reward system (in particular the six-month SPC extension), which delays the market entry of cheaper generics and pushes up total healthcare expenditure. These extra costs are borne by the healthcare system and individual patients (directly or through their contribution to healthcare-related taxes and health insurance).

The cost-benefit analysis[257] looks at the benefit-cost ratio over 10 years for the eight medicinal products that received a PIP-related SPC extension and which were considered

253 Article 48 of the Paediatric Regulation.

254 Commission Staff Working Document on the evaluation of the European Medicines Agency's fee system.

255 The costs of PUMA-related fee incentives are fully borne by the EMA.

256 Section 2.1 of the EMA fee system study.

257 Details can be found in Annex 3. Study on the economic impact of the Paediatric Regulation, including its rewards and incentives – Final Report, December 2016: Chapter 6.

previously.[258] Five of these are used on-label in children, while for the other three data indicate continued off-label use in children after negative PIP studies.

The cash and non-cash benefits for society and child health can be estimated at €199 million. The extra costs to society arising from companies' monopoly rent, to which revenue received by other beneficiaries, like wholesalers, and taxes must be added, can be estimated at €590 million.[259] Of these, €551 million are estimated to be costs incurred by national health services. This gives a negative ratio overall. Only two of the eight products considered had a strongly favourable benefit-cost ratio. The negative benefit-cost ratio was highest for products with negative PIP studies, as they do not provide any alternative treatment options for children.[260]

A broader basket of products was also assessed by estimating the future benefits and costs of products that had passed the Agency compliance check and been authorised. This basket also included products which, though required to comply with the PIP obligation, would not receive a SPC extension. These PIPs would result in paediatric products that did not involve costs to society associated with additional monopoly rent.[261] In such a simulation, the benefit-cost ratio for society remains negative, though less so (€500 million versus €590 million).

The impact assessment expected that direct benefits from the Regulation, such as the reduction of adverse effects or shorter hospitalisations, would offset costs incurred through delayed generic entry. However, indirect effects were not taken into account.

The economic spill-over effects resulting from the private R&D investments generated by the Paediatric Regulation are dealt with in the risk-benefit analysis detailed in Annex 3, section 4.7 of the paediatric part. On the basis of companies' annual investments in PIP-linked R&D of about €2 billion, the total return on investment to society after 10 years was estimated at €6 billion. This figure is significantly higher than the estimated monopoly costs linked to the SPC extension (€590 million).[262]

5.2.5. Inefficiencies of the Paediatric Regulation

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258 Sufficient data were available for only eight medicinal products to conduct the CBA. See Section 6.2.1 of the Paediatric study report (December 2016).

259 Study on the economic impact of the Paediatric Regulation, including its rewards and incentives – Final Report, December 2016: Chapter 6.3.5

260 Study on the economic impact of the Paediatric Regulation, including its rewards and incentives – Final Report, December 2016: Chapter 6.2.

261 Study on the economic impact of the Paediatric Regulation, including its rewards and incentives – Final Report, December 2016: Chapter 6.3.5.

262 Study on the economic impact of the Paediatric Regulation, including its rewards and incentives – Final Report, December 2016: Chapter 6.4, Table 28 in particular. For simplicity, it was assumed that the rate of return over the years would be linear, with a maximum cumulative return on investment 10 years after the initial R&D investment. However, in practice the spill-over effects are expected to be highest in the earlier years and to follow a decay curve.

The analysis above identifies several inefficiencies that could be addressed.

First, the SPC extension is awarded even if the outcome of the PIP is negative. This means that during the 'protection period' society cannot benefit from new paediatric treatments and the entry onto the market of cheaper generics for the adult medicine is delayed. This approach seems to have led to additional costs to society and patients, without any direct additional benefits. However, it is important to remember that a negative PIP still provides relevant data on the potential danger of the use of the product in children.

The reason for the second inefficiency is that paediatric medicines are developed worldwide, so companies often submit parallel requests for marketing authorisation in several countries. Lack of coordination between the requests made by various regulatory agencies in different parts of the world for the specific characteristics of studies to be conducted in children may lead to duplications of research.

To address this issue, the Agency created a 'paediatric cluster' in 2007, a monthly exchange between global regulators to discuss the coordination of their actions, first with the FDA and later joined by Japan, Canada and Australia. The objective is to enhance the science of paediatric trials and to avoid undue exposure of children to them. The benefits of this data sharing are a reduction in regulatory costs for companies and increased efficiency. The Agency-Commission joint paediatric action plan provides for further improvements in international cooperation.

Third, the Paediatric Regulation obliges companies to conduct paediatric research for each marketing authorisation application, unless a waiver is deemed appropriate. The small population size may often lead to competition between companies, if several target the same patient group for their respective research programme. This may lead to delays in completion and push up costs.

The 2016 economic study compared the costs of paediatric clinical trials in the EU and the US, both as enrolled study subjects, and as individual paediatric investigations (associated with developing a medicine) and clinical trials.[263] For the EU, cost estimates were based on information on individual PIPs and data on both completed and incomplete R&D phases. US cost estimates were based on data from two prominent studies published in the US. The cost of a paediatric investigation averages €21 million in the US and €18 million in the EU. As regards individual paediatric studies, the estimated amounts were €7 million in the US and €6 million in the EU. The study acknowledged that there were large

[263] Study on the economic impact of the Paediatric Regulation, including its rewards and incentives – Final Report, December 2016. Chapter 2.3.

variations in the sample dataset underlying the cost estimates, so significant uncertainties remained in these estimates. However, it noted that the cost estimates match.[264] [265]

The new Regulation on clinical trials,[266] which has not yet entered into force, is intended to streamline procedures for getting a clinical trial approved in Europe, particularly for multinational trials. It may help boost efficiency in conducting paediatric clinical trials.

5.2.6. Administrative burden

The administrative burden for developers associated with the Orphan Regulation has not been further substantiated, given the assumption that application of the Orphan Regulation is voluntary.[267]

The Regulation is responsible for some administrative burden at Agency level. These costs are relatively small but are likely to increase as the number of applications continues to grow. The issue of increasing workload also affects the national competent authorities contributing to the work of the COMP. The burden associated with the work performed by COMP members falls largely on their home institutions, which currently receive no financial compensation for that work in the absence of fee revenues.[268]

Lastly, some of the Agency's procedures create additional administrative burden, the necessity and proportionality of which should be examined (e.g. the obligation for sponsors to submit an annual report on the orphan designation to EMA).

As regards the *Paediatric Regulation*, stakeholders say the PIP application and related administrative procedures consume significant resources,[269] especially the frequent modification of an agreed PIP. Streamlining the PIP process is one of the measures considered in the joint Agency-Commission paediatric action plan.[270]

The inefficiencies associated with the functioning of the SPC reward procedure are another aspect. The SPCs are granted at national level, meaning that paediatric SPC extensions must be requested independently from the national patent office in each Member State.

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264 Study on the economic impact of the Paediatric Regulation, including its rewards and incentives – Final Report, December 2016. Section 2.3.

265 Li, J.S. et al., 2007. Economic Return of Clinical Trials Performed Under the Pediatric Exclusivity Program. JAMA, 297(5), pp. 480–488; Baker-Smith, C.M. et al., 2008. The economic returns of pediatric clinical trials of antihypertensive drugs. American Heart Journal, 156(4), pp. 682–688.

266 Regulation (EC) 536/2014 on clinical trials on medicinal products for human use.

267 Unlike the obligations under the Paediatric Regulation.

268 How this affects the fees system and the Agency's long-term sustainability was assessed in the 2019 evaluation of the Agency's fee system. See: https://ec.europa.eu/health/human-use/legal-framework/ema_fees_en

269 Study on the economic impact of the Paediatric Regulation, including its rewards and incentives – Final Report, December 2016: Chapter 4.3).

270 https://www.ema.europa.eu/en/documents/report/european-medicines-agency-european-commission-dg-health-food-safety-action-plan-paediatrics_en.pdf

Each patent office handles applications independently, which may result in divergent decisions.

Some patent offices receive specific training on the SPC procedure under the national regulatory system (e.g. in the Netherlands). This has improved the way these offices deal with SPC submissions.[271] A separate evaluation of the SPC system is currently under way.

From the perspective of public authorities, one particular area that merits attention is the growing administrative burden imposed on the national competent authorities of PDCO members (absences, workload). Since the Regulation took effect, the number of procedures (especially PIPs, modifications, waivers, deferral) has increased, pushing up PDCO's workload as a result. While there is no evidence that this has adversely affected the quality of assessments, the long-term impact on the proper functioning of the system is unknown.[272] In the short term, the ongoing Agency-Commission paediatric action plan seeks to find ways to streamline some of these procedures, to reduce the burden on the committee.

[271] Study on the economic impact of the Paediatric Regulation, including its rewards and incentives – Final Report, December 2016: Chapters 4.3 and 4.5.

[272] 10 years of the EU paediatric regulation, report from the Commission to the European Parliament and the Council, (COM(2017) 626, Section 9.

5.3 RELEVANCE

Main findings

The specific objectives of the Orphan and Paediatric Regulations have proven relevant to addressing the problems that existed when the legislation was adopted, and still exist today.

The narrow problem definition on which the orphan legislation is based was not well thought out and was thus inappropriate for addressing wider and more recent needs, such as treatments for infectious diseases. As a result, the current legislation is less relevant than it might be.

The objectives of both the Orphan Regulation and, to some extent, the Paediatric Regulation, have evolved over time. When the Orphan Regulation was designed, the priority was to bring products for patients with rare diseases to the EU market. Today, any legislative intervention in this policy area would also need to guarantee equal access to medicines across the EU. Moreover, the market for orphan medicines has become more financially attractive, as evidenced by the number of companies with orphan medicines in their portfolio. This changing context calls into question whether the system of rewards and incentives instituted by the Regulations remains relevant to current needs.

Finally, ongoing and future developments, both scientific and non-scientific, in the pharmaceutical sector, especially in the field of advanced therapies, personalised medicine and innovative trials design, will have significant implications for the Regulations' relevance in the future. These new products, which challenge the system of orphan designation, call for policy changes in defining orphan condition and deciding which subset(s) to take into consideration when applying for orphan designation.

To assess the relevance of these two Regulations, we need to analyse whether the objectives and tools they set out were and are appropriate to tackle the problems that *existed*, the issues that are being faced *now*, and challenges in the near *future*.[273]

At the time of the intervention, the problems were identified as a lack of treatment for patients with rare diseases and of medicines specifically studied and developed for children. The legislation therefore focused on these two groups.

Looking at the objectives of each of the instruments, they can be seen as adequate responses to the problems identified at the time. Making medicines for rare diseases available by fostering research and development, and providing the same quality of treatment for patients with rare diseases, certainly addressed the needs of the patients concerned. Research on and testing of medicines for children and providing information about those medicines addressed the lack of targeted medicines for children.

[273] See also the description of the intervention and its objectives in Chapter 2 of this SWD.

Looking at the problem today, it becomes obvious that the lack of treatment is broader. Lack of treatment affects not only rare diseases, but also infectious diseases. On the one hand there are known diseases for which existing antibiotics no longer work, owing to the development of antimicrobial resistance. On the other hand, there are new diseases, in particular viral diseases, for which adequate medicines have yet to be developed. Since the 1970s, newly-emerging diseases have been identified at an unprecedented rate of one or more a year. There are now nearly 40 diseases that were unknown a generation ago.[274] More research is needed to develop new medicinal products and alternative treatments, as well as innovative anti-infective approaches to tackle this emerging threat.[275] The narrow problem definition used as the basis of the orphan legislation has proven inadequate to address those needs.

The tools of both legal instruments were designed to address the root cause identified at the time: market failure (in particular, the fact that the target group of patients was too small to generate a profit). They were designed to create financial incentives for industry to invest in research, development and clinical trials on medicines in both target groups.

The results in the effectiveness section have shown that the root cause, low expected return on investment, still exists. The comparative analysis shows that turnover levels for orphan medicines can be lower than those of non-orphans, sometimes significantly so. However, this does not necessarily apply to the whole target group as defined in the legislation. The orphan medicine market has become more financially attractive, as proven by the number of companies with orphan medicines in their portfolio and the interest that venture capitalists show in investing in this field.[276] This has resulted in the development of medicines in some therapeutic areas where treatments already exist, while other areas have none. Rare diseases can thus no longer be viewed as a homogeneous group for which no treatments are available, and may need more differentiated tools to direct investments to the areas where they are most needed.

Although antibiotics were not included in the initial consideration of needs and problems, the root cause of low return of investment applies here as well. Pharmaceutical companies are unwilling to invest in developing new antimicrobials because of concerns about non-profitability. In fact, new antimicrobials would need to be developed and kept on the shelf for reasons of antimicrobial resistance.[277] This means there is no market in practice, so companies have no interest in developing new antimicrobials which would bring them no return on investment. Based on this analysis, antibiotics could be assigned an orphan designation under the 'low return on investment' criterion in the legislation. However, that tool has not so far boosted investment in this field. This shows that the tools currently

[274] https://www.who.int/whr/2007/overview/en/index1.html
[275] A European One Health Action Plan against Antimicrobial Resistance (AMR): https://ec.europa.eu/health/amr/sites/amr/files/amr_action_plan_2017_en.pdf
[276] Section 6.4 of the Orphan study report (2019).
[277] https://ec.europa.eu/health/amr/antimicrobial-resistance_en

available are not fit for purpose. A more in-depth assessment of root causes, along with appropriate tools to tackle the lack of investment, is needed in the area of antimicrobials.

In paediatrics, findings on effectiveness show that rewarding companies for testing medicines for use in children boosted the development of paediatric medicines linked to medicines for adults. However, therapeutic areas involving diseases that affect only children have been left behind. More differentiated tools may thus be needed for paediatrics as well, to direct investments where they are needed most.

The objectives of the orphan and paediatric legislation also implied that an EU authorisation would translate into medicines being accessible to patients in all Member States. However, the tools for progressing beyond the authorisation stage were limited. The legislation relied on industry decisions to make medicines available in each Member State. The main influences on such decisions are companies' strategic decisions on the one hand, and national pricing and reimbursement policies on the other. However, the legislation contains no provisions that could influence those stages. Although the legislation achieved the objective of making medicines available, it fell short of achieving affordable medicines that are accessible to patients in all Member States.

Progress in science and the changing context

Science has also moved on over the last 20 years, and the tools provided by the two Regulations may no longer be appropriate in the light of these advances.

New types of products and production techniques

While science evolves, the opportunities it provides also increase. The tools laid down in the legislation were designed in line with the approaches to developing and authorising medicines that prevailed at the time. For new types of medicines that do not follow conventional approaches, this may pose challenges.

Advanced therapy medicinal products (ATMPs) and biological medicines account for a growing proportion of all EU orphan designations.[278] They offer many therapeutic advantages in the treatment of rare diseases, particularly those which have the potential to cure such disorders, but also pose challenges as regards applying the Orphan Regulation framework. This framework relies on criteria which must be met if a product is to receive an orphan designation. This designation should ensure that only products addressing a rare disease fall under the scheme. It should also reward development by granting exclusivity, unless a significant benefit can be demonstrated by the new product (or clinical superiority in the case of a similar medicine).

[278] See Chapter 2.1. of this SWD.

ATMPs may reach the market with limited clinical data via conditional marketing authorisations. The conditional marketing authorisation makes it difficult for COMP to assess at the time of initial authorisation whether the product offers any significant benefit over and above existing treatment options, and hence whether the orphan designation can be confirmed and the company can profit from market exclusivity. In addition, this form of authorisation also challenges the step after the conditional authorisation when Member States need to decide how to price the medicine and provide reimbursement. In targeted surveys, representatives of HTA institutions and Member States have indicated that the limited evidence at the time of granting the conditional marketing authorisations represents a real challenge for assessors who need to determine whether a product is cost-effective and should be admitted into reimbursement systems.[279]

Over the last 20 years there have been numerous advances in genomic research, making it possible to better define diseases and understand the molecular causes of complex diseases. This change is not new per se but is in constant evolution. The fact that subtypes of new diseases are being identified that were previously thought to be part of a broader disease is beneficial to patients and researchers. In the context of rare diseases, **personalised genomic approaches** are particularly relevant, as an estimated 80% of rare diseases have a genetic component. With personalised medicine becoming increasingly developed, it could be at the forefront of clinical applications within the next 20 years.

The personalised medicine approach has already shown to be highly cost-effective, with new medicines now available that target, among others, rare diseases such as rare melanoma and cystic fibrosis in patients carrying specific mutations. As mentioned in the Council conclusions of 7 December 2015 on personalised medicine for patients[280], personalised medicine is not only about medicines (pharmaceuticals/medicinal products) but rather about putting the person at the centre of healthcare by better understanding the genetics, the detailed biological mechanisms and interactions with the environment, therefore facilitating the discovery and development of effective treatments for rare and common diseases alike.

Personalised medicine does not change the definition of the disease, but targets better the patient population responding to a certain medicine. Therefore developments in personalised medicine should not lead to unnecessary multiplication of rare diseases out of common diseases and hence to multiplication of exclusivity periods.

The EU's experience with applications **for orphans defined by biomarkers**[281] shows that although they can define a valid sub-set of a condition acceptable for orphan designation,

279 Section 7.2.4. of the Orphan study report (2019)

280 http://data.consilium.europa.eu/doc/document/ST-15054-2015-INIT/en/pdf

281 The Agency defines a biomarker as '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.' https://www.ema.europa.eu/en/glossary/biomarker.

there is still a need to demonstrate medical plausibility and significant benefit in the defined condition. The fact that the medicine concerned does not work outside the sub-set it is being developed for must also be demonstrated. However, establishing the absence of efficacy is generally challenging and not a primary goal in the development of medicines (which focuses primarily on establishing safety and efficacy). It is therefore challenging for applicants to provide robust evidence that a product is not efficacious outside a specific sub-set.

In addition, biomarkers are increasingly used in what is known as tissue-agnostic development in oncology, where the product development is not focused on patients with a particular type of cancer, but rather on any patient expressing particular biomarkers, independent of the tissue or origin of the cancer. Treatments developed this way may display activity against multiple types of cancer or subsets thereof, which would require changes to the policy on defining the orphan condition and on which subset(s) should be taken into consideration when applying for orphan designation.

In the US, the use of sub-setting orphan designations through biomarkers is becoming more widespread, particularly in the field of oncology. Between 2009 and 2015, 28% of oncological orphan medicines there were based on biomarker-defined subsets. This represented 12% of all new oncology medicines authorised in that time period. However, as reflected above, opening the EU system to more sub-setting may not bring more developments in areas where there is no treatment available, but could put further strain on national reimbursement systems.

New ways of conducting clinical trials

There have also been major developments in how clinical trials are designed and conducted since the introduction of the Orphan and Paediatric Regulations. These developments can benefit both pharmaceutical companies and patients by improving research productivity and accelerating the rate at which new treatments are brought to market, while also reducing the burden on patients. However, some of these developments affect the way both Regulations can be applied, including the work of the Agency Committees.

For example, basket trial designs are designed around a mechanism of action, providing evidence on the mechanism of action rather than efficacy as such. As the sample sizes within each basket are small, COMP may find it challenging to estimate significant benefit. Furthermore, in cases where basket trials address a novel mechanism of action that presents itself differently from the description in the existing definition of the condition, this can pose challenges in the EMA authorisation procedure similar to the one described above.

As regards the Paediatric Regulation, these novel ways to conduct clinical trials may have a direct effect on the PIP, which requires applicants to submit paediatric investigation plans very early in the development phase. An early design of a PIP creates opportunities for

discussion of paediatric matters early on in the development of a product. However, in some cases it may be challenging to consider and design all aspects of medicine development for children in the very early phases of development. This is especially true in the case of innovative and adaptive clinical trials design. This may lead to a subsequent need to amend the agreed paediatric investigation plan several times, which increases the administrative burden and may even delay authorisation. Some of the measures set out in the joint Agency-Commission paediatric action plan[282] are designed to further explore whether there is a non-legislative way of addressing this issue.

To conclude, scientific developments will mostly have a clear positive effect on the potential for developing new treatments for patients with rare diseases. At the same time, they may challenge the framework and application of the Orphan Regulation and, to a lesser extent, that of the Paediatric Regulation. It is therefore important for the regulatory framework to be kept sufficiently up to date with such developments and their potential consequences, so that the framework can capitalise on opportunities while limiting potentially unwanted effects. A main area of tension where the Regulation is being challenged as a result of scientific advances is the definition of an orphan condition.

5.4 COHERENCE

Main findings

The Orphan Regulation offers a set of incentives that work well together and it is relevant to both smaller and larger developers. The fee waivers, protocol assistance, market exclusivity and support for research complement one another. However, better alignment of timing and information needs between the four Agency Committees dealing with orphan and paediatric medicines could reduce the risk of inefficiencies.

The Orphan Regulation and national research programmes and policies complement and support each other to a large extent. However, there is no monitoring to enable the interplay between EU research funding and the Orphan Regulation to be assessed. More specifically, there are no indicators to demonstrate how public research investments contribute to successful authorisations of orphan medicines. Furthermore, the Orphan Regulation does not interact in a coherent fashion with the Directive on Medicinal Products for Human Use (2001/83/EC) as regards generic entry. The Orphan Regulation only allows developers of generic medicines to initiate an application for a marketing authorisation once the market exclusivity period has expired.

The Paediatric Regulation mostly interacts in a coherent manner with related EU and national legislations and measures. However, national rules on the conduct of trials with children may still delay the completion of a paediatric investigation plan (PIP). Moreover,

[282] https://www.ema.europa.eu/en/documents/report/european-medicines-agency-european-commission-dg-health-food-safety-action-plan-paediatrics_en.pdf

as regards the SPC extension reward, the fact that this incentive is granted by national patent offices that act independently makes it difficult for companies to forecast whether this can be done successfully. An improvement in the situation for multinational paediatric trials can be expected with the application of the new Regulation on clinical trials and the implementation of the joint Agency-Commission paediatric action plan.

The combined application of the Orphan and Paediatric Regulations has not provided sufficient incentives to foster the development of new innovative medicines for use in children with rare diseases.

In evaluating how the two Regulations fit within a broader over-arching architecture, the degree of consistency between the provisions of each Regulation was analysed (*internal* coherence). How they relate to other EU (legislative and non-legislative) and national actions (*external* coherence) was also assessed.

Internal coherence

Orphan Regulation

The various tools provided by the Orphan Regulation work well together to support the development of new orphan medicines. No barriers, overlaps or contradictions were identified. Responses to targeted consultations suggest that the various tools of the Orphan Regulation work together in a coherent manner. The sponsors interviewed said that each tool or incentive served a specific purpose, addressing different aspects and pressure points across the innovation lifecycle. The fee waivers, protocol assistance, market exclusivity and support for research (or for encouraging research) have created a stronger policy response to unmet medical needs than any one of those incentives would have done in isolation. They seem to function in synergy and are not disconnected or confused, according to the interviewees.

Paediatric Regulation

The overall system of obligations and rewards put in place by the Paediatric Regulation is perceived by all the stakeholders interviewed as working in a coherent way.[283] [284] This was also confirmed by the data, as analysed in the effectiveness section.[285]

[283] Public consultation on the Paediatric regulation conducted in 2016).
[284] Section 4.2 of the Orphan study report (2019).
[285] Chapter 5.1 of this SWD.

However, the fact that the SPC extension is granted by national patent offices that act independently and the timelines for applying for such a reward make it difficult for companies to predict whether the outcome of their request will be successful. Furthermore, the SPC extension leads to higher rewards if paediatric development is linked to adult development (a detailed analysis is provided in the effectiveness section).[286]

Agency committees[287]

A product may be assessed by up to four[288] Agency committees: COMP for the orphan designation, PDCO for approval of the PIP, CHMP for the benefit-risk assessment required for marketing authorisation, and in the case of ATMPs, CAT has the primary responsibility for the assessment of the application (but the final opinion is adopted by CHMP). CHMP can also grant conditional marketing authorisations on the basis of less comprehensive data.[289]

The overall opinion[290] of members of the committees was that the committees work reasonably well together and that there are no major issues.

However, a few areas were identified where there had been occasional challenges,[291] which may also lead to inefficiencies:

- CHMP, PDCO, CAT and COMP use different timelines for their assessments and sponsors submit different data to each committee. This can make scientific discussions difficult as they lack common ground, which can adversely affect the outcome or the timing.[292]
- The timelines associated with decision-making are different for CHMP/CAT and COMP. As a result, the COMP process is not well integrated in the CHMP/CAT process, which may lead to delays in some cases.
- In addition, while it is PDCO that decides on the PIPs, the decision on the orphan designation is taken by the Commission, based on a scientific opinion from COMP. This adds more time to the process.

The majority of developers of orphan medicinal products were broadly positive in the targeted consultation about the coherence of the various committees' activities. The clarity of communication and on time assessments were widely rated as being coherent. However,

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286 Section 5.2 (Effectiveness) of this SWD.
287 Section 9.3 of the Orphan study report (2019).
288 Depending on the type of product and orphan indication.
289 Commission Regulation (EC) No 507/2006. This Regulation stipulates that to meet patients' unmet medical needs and in the interests of public health, it may be necessary to grant conditional marketing authorisations ('CMAs') on the basis of less comprehensive data than is normally the case.
290 Section 9.3 of the Orphan study report (2019).
291 Idem.
292 For example, PDCO and COMP may look at the same product development without any formal interaction.

the respondents were less positive about the consistency of outcomes, especially the alignment and coherence of procedures among committees.

External coherence

Orphan Regulation

- *Other legal instruments*

The *Orphan* Regulation interacts with other EU legislative acts, mainly Directive 2001/83/EC on Human Medicinal Products, the SPC Regulation and the ATMP Regulation.[293] Developers of orphan medicines can benefit from incentives and rewards offered by each of these legal instruments, depending on the product characteristics of the new medicine. However, while the data and market protection periods applicable to all human medicines[294] would allow generic competitors to *place* generics on the market at the end of the 10-year protection period, for orphan medicinal products[295] generic competitors can only submit an *application* for marketing authorisation at that point in time. This may delay generic entry.

Developers of orphan medicinal products say that the protections offered by the SPC and the Orphan Regulation have benefited pharmaceutical innovation and the development of orphan medicines in particular. They did not report any specific tensions between the operations of the two Regulations.[296]

- *EU and national research initiatives and programmes*

The Orphan Regulation states that medicinal products designated as orphan medicinal products are eligible for incentives made available by the Community and Member States.[297]

EU research incentives

A variety of EU initiatives and programmes exist that support the development of treatments for rare diseases. The EU has made major investments during the last two decades to support cross-border and interdisciplinary research in almost all medical fields including rare diseases, which has contributed to the understanding of the underlying causes of these diseases and to the development of diagnostics and treatments. Since 2000, more than €1.7 billion has been made available, via the EU Framework Programmes for

293 See also Section 2.1 of this SWD.
294 Article 10 of Directive 2001/83/EC).
295 Article 8(1) of the Orphan Regulation.
296 Section 9.1.1. of the Orphan study report (2019).
297 Aid for research into the development and availability of orphan medicinal products (Article 9(1) of the Orphan Regulation).

Research, Technological Development and Innovation (FP5, FP6, FP7 and Horizon 2020), to over 340 collaborative research and innovation consortia (projects) in the area of rare diseases.[298] Such research projects bring together multidisciplinary teams representing universities, research organisations, SMEs, industry and patient organisations from across Europe and beyond.

Table 8: EU budget allocated to collaborative research & innovation projects on rare diseases

Framework Programme	Timeframe	EU contribution, millions of euros	Number of projects addressing rare disease(s)
FP5	1998-2002	64	47
FP6	2002-2006	233	59
FP7	2007-2013	>624	>118
H2020	2014-2019	>808	>137

Source: DG RTD (data available up to January 2020)

The field of research into rare diseases has been a good example of success, showing how further investments and resources from across Europe can be brought together to a degree that would not reasonably be possible within an individual Member State, or even a sub-set of Member States acting in isolation. These activities have increased the scale of investment by the public sector in rare disease research.[299]

EU-financed private-public partnerships under the 'Innovative Medicines Initiative'[300] have also supported projects, thereby speeding up R&D of medicines for rare diseases. The ULTRA-DD project,[301] for instance, was designed to produce new tools and resources to speed up the development of orphan medicines, especially in the areas of autoimmune and inflammatory diseases.

In addition, European Reference Networks (ERNs)[302] play an increasingly important role, not only in research, but also in sharing information to improve diagnosis and the quality of care, as well as in providing clinical practice guidelines in medical fields where expertise is rare.[303] [304] ERNs are expected to have a major structuring effect on research and care by

298 On the basis of DG RTD data.

299 Section 10.5 of the Orphan study report (2019).

300 IMI is a joint undertaking between the European Union and the European Federation of Pharmaceutical Industries and Associations (EFPIA). The focus of research under the IMI umbrella has been partly led by industry (https://www.imi.europa.eu/).

301 https://www.imi.europa.eu/projects-results/project-factsheets/ultra-dd

302 Virtual networks involving healthcare providers across Europe that were established in 2017 and are financed under the EU health programme (https://ec.europa.eu/health/ern_en).

303 Most ERNs cover adult and paediatric conditions, but some of the thematic networks included in the project focus on rare paediatric diseases.

304 See also the introductory chapter of the Special Report of the European Court of Auditors ('EU actions for cross-border healthcare: significant ambitions but improved management required', 2019).

linking thematic expert centres across the EU and providing sustainable clinical networks to pool medical expertise and patient registries' data on rare diseases.

However, an important question is whether all this public funding spent on research has led to available and accessible new orphan medicines covering an unmet medical need. The information available did not provide sufficient data to answer this question, as there is no legal obligation to follow the development of the product after the first research is conducted. The EU has limited influence over the direction of the research it supports through these programmes. Interplay between these research funding programmes and the EU Orphan Regulation is not monitored or reported in any formal sense. Moreover, research funding agencies (in both Europe and the US)[305] lack quantitative performance indicators to demonstrate the direct correlation of public research investments with the impact of research on society, in terms of benefit to patients (e.g. new treatments, diagnostic tools, rare diseases identified, and orphan medicinal products developed). Often, research does not produce results until several years after the end of the funding period.

At the moment, the funding itself can only be linked to the obligation to have obtained an orphan designation, a prerequisite that has existed since 2009 for receiving Framework Programme funding.[306] There was been a rise of over 50% (see Figure 5 in Chapter 5.1 of this SWD) in both the number of orphan applications submitted and the number of designations granted by the Commission over 2009-2015 (against 2000–2008). In particular, a Horizon 2020 call for Phase I/II clinical trials on rare disease therapies with an orphan designation led to a peak in the number of applications between 2014 and 2016.[307] However, it is still too early to see results in the new orphan medicines authorised.

Another example of EU research funding is the AlphaMan project,[308] leading to the development of an enzyme-replacement therapy for a rare genetic disease called alpha-mannosidase. This resulted in the EU marketing authorisation of Lamzede[309] in 2018, the first ever treatment for this condition.[310]

A non-exhaustive list of successful EU projects can be found on the dedicated DG Research website.[311]

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305 Based on information from DG RTD.

306 See Chapter 3.3 of the Inventory of Union and Member State incentives to support research, development and availability of orphan medicinal products (SWD(2015) 13 FINAL).

307 Section 9.4 of Orphan study report (2019). See also Figure 3 in Chapter 5.1 of this SWD (effectiveness) with the number of designations granted per year (2000 – 2017).

308 ALPHA-MAN (Clinical development of Enzyme Replacement Therapy in alpha-Mannosidosis patients using recombinant human enzyme.)

309 Official Journal of the European Union, C 150, 27 April 2018.

310 Section 9.4 of the Orphan study report (2019).

311 https://ec.europa.eu/info/research-and-innovation/events/special-features/world-rare-diseases-day_en

Member States' research initiatives

It was also explored how the Orphan Regulation aligns with related measures taken at *national* level by Member States.

The number of Member States with a national plan supporting rare disease research into the development and availability of orphan medicinal products has grown substantially since 2009.[312] In that year, only four Member States had a national plan or strategy, whereas by 2017 the number had increased to 23 countries.[313] There was, however, no data available to further explore the link between these plans and the orphan designations and authorisations granted.

Paediatric Regulation

The Paediatric Regulation also interacts with EU legislation on the supplementary protection certificate for medicinal products ('SPCs') (Regulation (EC) 469/2009) and on clinical trials (Directive 2001/20/EC).[314]

- *SPC legislation*

As the Paediatric Regulation provides for the possibility to receive an extension of six months of the SPC when a PIP is conducted, any modernisation or recalibration of the SPC system following the ongoing evaluation of the SPC regulation[315] will influence the paediatric reward system. Any inefficiencies in the SPC extension system that are identified could be addressed in possible future measures following up that evaluation.

- *Clinical trial legislation*

The Paediatric Regulation resulted in an increase in paediatric clinical trials. The instrument for ensuring that such clinical trials are conducted, respecting the ethical principles[316] for protecting minors from unnecessary testing, and involving children in the decision to participate in a trial or not, is the EU Clinical Trials Directive and Regulation.[317]

312 The EPSCO council recommended the establishment of national rare disease plans in 2009.
313 Section 9.5 of the Orphan study report (2019).
314 The SPC Regulation is designed to offset the loss of patent protection for pharmaceutical products that occurs due to compulsory testing and clinical trials before a marketing authorisation can be obtained. The Clinical Trials Directive provides a legal framework for the conduct of clinical trials in Europe and contains specific provisions on clinical trials conducted with the participation of minors.
315 https://ec.europa.eu/growth/industry/intellectual-property/patents/supplementary-protection-certificates_en
316 Recital 7 of the Paediatric Regulation.
317 Directive 2001/20/EC (a new Regulation (EC) No 536/2014 on clinical trials was adopted in 2014, but has not come into force yet).

[318] In substance, the Paediatric Regulation and the EU Clinical Trials legislation can be considered complementary.

However, when a PIP is agreed and the clinical trials need to be approved and conducted, several problems have been reported, such as divergent ethical views at national level on the conduct of trials with children, including requests to delay the conduct of trials with children until after data from adults become available.[319] This may result in companies requesting a deferral of PIPs (or part of them), and consequently in delays in developing medicines for children.

While it is essential that trials are conducted in accordance with strict ethical principles and protect the safety of children, it is considered necessary for assessors to be better aware of the requirements of the Paediatric Regulation and the reasons for the various PIPs.[320] The joint Agency-Commission Paediatric Action Plan provides for measures to tackle these issues.[321] Moreover, the new Clinical Trial Regulation will further harmonise the conduct of multinational trials and increase paediatric expertise in the evaluation of clinical trials. This new legislation is consequently expected to help find solutions to those problems.

- *EU non-legislative activities*

In addition to identifying certain shortcomings of the Regulation, the Report on the 10 years of experience with the Paediatric Regulation[322] has also identified short-term measures designed to try to improve the implementation of the Paediatric Regulation. To follow up, on such points the joint action plan on paediatrics has been developed to respond to such conclusions.[323]

- *EU-funded research*

The impact assessment of the Paediatric Regulation deduced that certain tools set up by the legislation, and in particular the PUMA scheme, should have been complemented by EU research funding. This has not been done via a dedicated fund to promote independent

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318 The date of application of the Regulation depends on the Agency's finalising a database that is necessary for its operation.

319 Multi stakeholder workshop on 'How to better apply the Paediatric Regulation to boost development of medicines for children', https://www.ema.europa.eu/en/documents/report/how-better-apply-paediatric-legislation-boost-development-medicines-children-report-multi_en.pdf

320 This issue was discussed during a multi-stakeholder workshop held in March 2018 to draw up the Agency-Commission joint paediatric action plan.

321 Topic areas 2 and 3 of the action plan: https://www.ema.europa.eu/en/documents/report/european-medicines-agency-european-commission-dg-health-food-safety-action-plan-paediatrics_en.pdf

322 State of Paediatric Medicines in the EU – 10 years of the EU Paediatric Regulation: Report from the Commission to the European Parliament and the Council (COM(2017)626).

323 https://www.ema.europa.eu/en/documents/report/european-medicines-agency-european-commission-dg-health-food-safety-action-plan-paediatrics_en.pdf

research into the use of substances not covered by a patent or an SPC, as set out in the impact assessment, but via the standard EU research programmes.[324] [325]

Furthermore, to complement the PUMA scheme, the Committee on Proprietary Medicinal Products Paediatric Expert Group (the predecessor of the PDCO) at the time of the preparation of the legislation developed a list of 65 off-patent medicines considered priorities for research and development. This list continues to be updated by the PDCO; by 2017, 23 projects on 28 off-patent medicines (active substances) had received EU funding.[326]

Despite having provided significant results in neglected areas, such tools to support research have not resulted in a parallel success of the PUMA scheme.

- *Other national initiatives*

Member States have also put in place other initiatives which complement the provisions of the Regulation.[327] These include priority review of paediatric clinical trials applications, and fee waivers for the authorisation of paediatric clinical trials (clinical trials are authorised at national level), which streamline the conduct of studies agreed in a PIP. Furthermore, special measures have been put in place to determine the pricing of paediatric medicines or measures to reduce the use of off-label medicines when paediatrically tested alternatives are available on the market.

- *International*

The development of medicines is often a global affair. Products are studied and marketing authorisations are requested in various regions. Cooperation between international regulators therefore aims on the one hand to exchange information on how to address similar requests and, on the other hand, to provide similar advice and opinions to companies. These activities are ongoing at international level, mainly in 'clusters'.[328] In the paediatric cluster, the Agency works together with the regulators from the US, Japan, Canada and Australia. In the orphan cluster, it works together with the US regulators.

Analysis of international paediatric activities suggests that the Agency and the FDA's joint approach to paediatric medicines (the EU and the US have very similar legislative frameworks in this area) has the potential to help reduce regulatory costs for companies in

[324] Article 40 of the Paediatric Regulation.
[325] In the US, the FDA manages a specific fund to support research in off-patent products.
[326] Agency's 10 years report (Section 3.6.1.)
[327] Idem.
[328] A discussion forum facilitating regulatory discussions on global development of paediatric medicines. It was set up in 2007 as a joint Agency/FDA venture; in 2009 and 2010, respectively, Japan and Canada joined, followed in 2014 by Australia as an observer.

future if they submit in parallel in both regions.[329] The Study on the economic impact of the Paediatric Regulation involved a survey in which companies were asked whether they also used PIP data for their applications to the FDA. This revealed that data from 54% of PIPs were used in some degree when applying to the FDA and/or were subject to ongoing discussions with the FDA.[330]

Coherence between the two legislations

As around 90% of all rare diseases manifest themselves in childhood,[331] there is a clear need to develop orphan medicines that also cater for children. The main concern raised by 'non-industry' stakeholders is the limited development of products suitable for children with rare diseases.[332] [333] As previously described,[334] the Orphan and Paediatric Regulations, both alone and combined, have not provided sufficient incentive to foster the development of medicinal products for children with rare diseases.

[329] Technopolis Study on the economic impact of the Paediatric Regulation, including its rewards and incentives – Final Report, December 2016 (SANTE/2015/D5/023, Section 2.3.1).
[330] Study on the economic impact of the Paediatric Regulation, including its rewards and incentives (section 2.3.1).
[331] Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database, European Journal of Human Genetics, 2019.
[332] Only half of all currently authorised orphan medicines have been approved for use in children as well (Section 7 of the Orphan study report (2019)).
[333] Section 9.1.2 of the Orphan study report (2019).
[334] Chapter 5.1.4 of this SWD.

5.5 EU ADDED VALUE

Main findings

The Orphan Regulation has enabled the parties concerned to respond in a more concerted and effective way to the challenges of developing orphan medicines. Alongside other measures, it has contributed to an increase in R&D activities in nearly all main therapeutic areas. Between 2000 and 2017, 1956 medicines under development were granted an orphan designation. This would not have been reasonably possible at the level of Member States alone, given the lack of sufficient economic incentives for R&D and limited ability to conduct clinical trials on small numbers of patients without sufficient research networks and researchers.

However, if one compares the increase in the number of orphan medicines on the market with the baseline situation before 2000, the added value of the Orphan Regulation is somewhat modest. In terms of time-to-market and availability of orphan medicines, there are substantial differences between Member States, and the added value has been comparatively low for some of them.

The *Paediatric* Regulation has created a positive trend in developing new medicinal products for children, similar to what has happened in the US from the 1990s on, after the introduction of paediatric legislation there.

Both Regulations respect Member States' exclusive competences in fields such as the administration of health services, pricing, and reimbursement. Overall, the Regulations work in synergy with other instruments, such as EU research programmes and legislative acts.

EU added value refers to the changes and results observed in the areas of orphan and paediatric medicines across the EU which could not have been achieved through action at regional or national levels. Ideally, EU added value would have been established through a comparison with a counterfactual scenario in which the Orphan Regulation was not implemented (for instance, by making comparisons with another region that is similar to the EU in significant ways, but which has not introduced specific orphan legislation). However, comparable regions like the US and Japan have all introduced broadly analogous policies. There was thus no candidate comparator or source of data on which to construct such a counterfactual situation for orphan medicines.[335] In this way, the Orphan Regulation differed from the Paediatric Regulation, for which such a comparison was possible.

The assessment of EU added value has relied mainly on desk research, specifically on comparisons with the situation in the EU before the Regulations took effect, and on a

[335] See Section 10 of the Orphan study report (2019).

'comparator analysis'.[336] The analysis was complemented by feedback from interviews and the outcomes of the targeted consultations.

Orphan Regulation

The question of whether the Orphan Regulation has generated EU added value is linked with the question of whether the results achieved surpass those which could realistically have been expected at Member States' level (i.e. through national interventions alone).

The Orphan Regulation was the first legislative act concerning rare diseases in the EU. It represented the start of the development of a coordinated EU strategy to diagnose, treat and care for citizens with a rare disease. In 2009, the European Council of health ministers[337] issued a recommendation for action in the area of rare diseases and recognised the topic as an important public health issue. It encouraged the drawing up and adaptation of national plans and strategies, measures to boost research, and the pooling of expertise at EU level. In 2009, a focus on rare diseases was relatively new and innovative in most Member States and only a few had national plans in place. By 2019, plans had been established in 25 Member States.[338] [339]

Stakeholders agreed[340] that the Orphan Regulation has catalysed the development and marketing of orphan medicines and that it has contributed in ways that would not have been possible at national level alone, even when aggregated across Member States. At all events, action taken at national level alone could have led to distortions of the EU internal market.

- *Subsidiarity*

The authorisation of medicinal products, including orphan medicines, is fully harmonised at EU level. Thus Member States could not, and cannot, introduce specific provisions at national level in this field.

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336 A 'comparator analysis' involves comparing the results achieved by the Orphan Regulation with those that might realistically have been expected without it. For more details, see Sections 2.2. and 7.3. of the Orphan study report (2019).

337 Council recommendation on an action in the field of rare diseases (2009/C 151/ 22) June 2009, https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:151:0007:0010:EN:PDF
Implementation report on the Commission Communication on Rare Diseases: Europe's challenges [COM(2008) 679 final] and Council Recommendation of 8 June 2009 on an action in the field of rare diseases (2009/C 151/02), COM (2014) 548; https://ec.europa.eu/health/sites/health/files/rare_diseases/docs/2014_rarediseases_implementationreport_en.pdf

339 http://www.europlanproject.eu/NationalPlans?idMap=1

340 Section 10.1 of the Orphan report study (2019).

Experience in the US and Japan had shown that a key element in an effective policy of supporting R&D for orphan medicines was the creation of an official system of recognition and granting exclusive rights and incentives for a specific period.[341]

The Orphan Regulation addressed the issue of small populations and market fragmentation directly by creating economies of scale to an extent that would not have been possible through individual national policy initiatives. The market for individual orphan medicines was and is too small even in the larger EU Member States, so any national initiative would have needed to provide substantial incentives for firms to change their investment behaviour.

The Orphan Regulation itself does not prevent Member States from offering additional types of incentives, such as tax rebates or prizes for successfully developed products in chosen areas. These instruments can be helpful, and are part of the measures offered under the regulatory frameworks for orphan medicines in the US and Japan[342] and in some Member States.[343]

Nevertheless, it was found that few EU countries offered specific financial incentives for developers of orphan medicines. Particularly for smaller Member States, it was unlikely that these incentives would have made a clear difference to the pipeline for orphan medicines.[344] [345] [346]

The Regulation appears to have respected Member States' exclusive competences, for example in the fields of administration of health services and pricing and reimbursement, as well as in setting taxes and tax incentives for companies. In addition, the provision of healthcare, including prescription of medicines, is the responsibility of Member States. Such national measures have had a major impact on the current accessibility of orphan medicines, as described in the effectiveness section.

- Proportionality

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341 See Communication/Explanatory Memorandum about Draft Proposal (introductory text and second recital on page 12); the success of the US orphan system had encouraged other countries to follow (p. 2 of the same document).

342 At the time, for instance, all designated orphan products in the US were eligible for a federal tax credit equal to 50% of the spending on clinical research (see p. 2 of the Communication/Explanatory Memorandum about Draft Proposal).

343 Belgium and France, for instance.

344 Recital 3 on page 12 of the Communication/Explanatory Memorandum.

345 Section 10.2 of the Orphan study report (2019).

346 EU added value was also recognised in the outcomes of the targeted survey. A majority of academic researchers and experts who participated in the survey agreed with a statement that, at the time when the EU Orphan Regulation was introduced, there was a clear need for concerted EU action beyond the efforts of individual Member States. Representatives of patient and consumer organisations also agreed with this statement (Section 10.2 of Orphan study report (2019).

The Orphan Regulation can be seen as a proportionate[347] response to what is a major challenge for all EU Member States, with more than 6000 orphan diseases affecting 35 million European citizens, many of them children.

As mentioned previously,[348] the Orphan Regulation leaves scope for individual Member States to continue playing their part in promoting the development of orphan medicines. Member States maintain the freedom to invest national funds in rare disease research.

Thanks to the Regulation, a European orphan decision-making system was created, without which the EU might have had to rely on products coming from other markets, such as the US or Japan. This could have adversely affected both the number of orphan products and their timely availability to EU patients.

EU legislation also catalysed national initiatives in the fields of rare diseases and orphan medicines. Individual initiatives by Member States in these fields could have led to distortions of the EU internal market.

Paediatric Regulation

- *Subsidiarity*

As with the Orphan Regulation, Member States could not and cannot introduce specific provisions at national level concerning the authorisation of medicines for children, as this area is fully harmonised at EU level.

The impact assessment conducted in 2004[349] showed that certain Member States had attempted to boost the authorisation of paediatric medicines by encouraging industry to conduct research in children and, where data on use of a medicine in children already existed, to submit applications for marketing authorisations. Such actions by Member States were largely unsuccessful, as they did not result in any increase in the number of paediatric medicinal products or authorised paediatric indications.[350] That was why an intervention at EU level was considered necessary.

The value of the EU legislative intervention can also be assessed by comparing regions that have legislation on paediatric medicines with regions that lack such legislation. The number of new paediatric medicines authorised between 2007 and 2015 in the EU and the US, which have similar paediatric legislation, is twice the number of new paediatric medicines authorised in Canada (which has a voluntary scheme), and is six times higher than in Japan (which has no comparable legislation).[351] These figures suggest that a specific

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347 Proportionality means that, to achieve its aims, the EU will take only the action it needs to and no more (see Article 5 of the Treaty on European Union).

348 Chapter 2.2.2 of this SWD.

349 https://ec.europa.eu/smart-regulation/impact/ia_carried_out/docs/ia_2004/sec_2004_1144_en.pdf

350 Extended impact assessment on medicinal products for paediatric use.

351 Agency's 10 years report, section 1.7

EU legal framework for paediatric medicinal products was necessary to boost the development of medicines for children.

Table 9: New paediatric medicines authorised in 2007-2015.

Region	EU*	US	Japan	Canada
New paediatric medicines	80	76	12	38
New paediatric indications	141	173	38	107
Total	**221**	**249**	**50**	**145**

Note: The data provided by other regions included medicines that are not subject to the obligations of the Paediatric Regulation. For the purpose of this analysis, these medicines (generics, hybrid medicines, biosimilars, etc.) were excluded.

*EU data include centrally authorised products and national/DCP/MRP products.

The Regulation appears to respect Member States' exclusive competences. Member States remain responsible for fixing pricing and reimbursement decisions, as well as for setting taxes and tax incentives for companies. Such national measures have a major impact in determining the current accessibility of paediatric medicines on the market.

Moreover, healthcare provision, including prescription of medicines, is the responsibility of Member States. Complementary actions taken by Member States include reviewing clinical trials and data for paediatric medicines, adopting national legislation to reduce off-label use, providing financial support to research networks that focus on developing paediatric medicines, encouraging internal cooperation between networks and connecting existing networks, and creating research infrastructure for studies in children.[352] [353]

- *Proportionality*

The Paediatric Regulation can also be viewed as a proportionate[354] response to the lack of appropriately tested and authorised medicines for children. At the same time, it allows scope for individual Member States to continue to play their part in promoting the development of paediatric medicines. Member States maintain the freedom to invest national funds in paediatric research.

It can therefore be concluded that the Paediatric Regulation has helped set a positive trend in developing new medicines for children, similar to what has happened in the US from the 1990s on after the introduction of a comparable legislative framework.

[352] Draft European Parliament and Council Regulation (EC) on medicinal products for paediatric use – DG Enterprise: Extended Impact Assessment (page 14); Final Report of the Study on the economic impact of the Paediatric Regulation, including its rewards and incentives (December 2016); Section 4.4.

[353] A list of medicine-related incentives and benefits provided by Member States can be found in Section 4.4. (Table 22) of the Final Report of the Study on the economic impact of the Paediatric Regulation, including its rewards and incentives (December 2016).

[354] Proportionality means that, to achieve its aims, the EU will take only the action it needs to and no more (see Article 5 of the Treaty on European Union).

6. CONCLUSIONS

New, innovative medicines are essential for providing new opportunities to treat or prevent diseases. Over more than 50 years, EU pharmaceutical legislation has established a framework that encourages the development of such medicines, while also ensuring high standards of quality and safety and enabling the internal market to function smoothly. However, efforts to encourage R&D in the pharmaceutical field may not necessarily have focused on the areas of highest unmet need; rather, it but may have followed scientific leads and market opportunities. Certain therapeutic areas are better served than others. This problem has long been acknowledged for conditions with small target populations, such as rare diseases or specific patient groups, such as children. More recently, it has also been discussed in relation to areas such as antibiotics.

Efforts made through funding research programmes did not succeed in addressing this issue convincingly. That was why additional legislative tools were considered necessary to support the development of medicines to treat rare diseases and for use in children and to promote greater patient access to such treatments.

The EU Orphan and Paediatric Regulations were introduced in 2000 and 2007 respectively. The Regulations provide a set of incentives for developers of orphan medicines and regulatory rewards accompanied by obligations for paediatric medicines. They are designed to address issues underpinning market failures in these areas.

This evaluation has assessed to what extent these two Regulations they have proven effective, efficient and relevant and bearing EU added value. It has compared the current situation with the situation in Europe before the application of the two Regulations and analysed how they have performed in comparison with the expected outcomes, taking the impact of external factors into account. The internal coherence of the actions of the two regulations as well as their interaction with other policies has also been assessed.

The Orphan Regulation

Since the adoption of the Regulation in 2000, 142 orphan medicines have been authorised, of which 131 have remained on the market. The number of marketing authorisations for orphan medicines has not only increased over time, but actually grown substantially faster than for non-orphan medicines. It cannot be claimed that all these 142 products were developed thanks solely to the Regulation. However, it is estimated that between 18 and 24 orphan medicines are direct results of this legislation. Moreover, access has been accelerated. All orphan medicines were available on average nine months earlier and to more people across the EU than would have been the case without the legislation.

Of the 142 authorised orphan medicines, 40 (28%) targeted diseases for which there were no alternative treatment options. The 142 authorised products have helped up to 6.3 million European patients out of roughly 35 million patients in the EU suffering from rare diseases.

This is major progress in comparison to 2000, when only a limited number of medicines for specific rare diseases were on the market (and only in some Member States).

The legislation has helped through incentives to redirect investment into neglected areas and to transform therapeutic discoveries into therapies for some patients, but there is a long way to go to meet the needs of all EU patients with rare diseases. Around 95% of rare diseases have no treatment option yet (the same is true in the US). Moreover, legislation cannot replace the need for scientific leads or breakthroughs in research in the first place.

The available figures in efficiency analysis suggest that the market for orphan medicines has become more commercially attractive than it was before 2000. The Regulation introduced a designation process which identifies the pipeline of orphan medicines and, with the prospect of market exclusivity, enables new companies to attract venture capital. Between 2000 and 2017, 1956 medicines under development were granted an orphan designation, covering a large spectrum of therapeutic areas, with anti-cancer treatments accounting for around a third of all designations and authorised products so far. This number indicates a clear positive impact.

However, the transformation from concept (i.e. orphan designation) to authorised orphan medicine remains slow, even bearing in mind that medicines have long development cycles of as many as 10 to 15 years. In this regard, the EU is still lagging behind the US and Japan. In addition, the US has authorised 351 orphan medicines over the last 10 years. Differences between the US and EU may be explained to some extent by the EU's two-stage process, in which orphan designations must be confirmed at the time of marketing authorisation (as opposed to the US's one-off designation). Japan's high approval ratio is consistent with the approach of designating only products with a strong chance of approval.

The Orphan Regulation uses a prevalence threshold (the condition must affect no more than 5 in 10,000 patients in the EEA) as an important criterion for products eligible for support under the Regulation. The evaluation results raise the issue of whether the current prevalence criterion (on its own) is still an appropriate way to define a rare disease, whether a different method for calculating prevalence is needed, or whether a different criterion should be applied. Advances in science, such as personalised medicine approaches and the use of biomarkers, already allow to better target treatments to responder patients. The concept of personalised medicine could add another layer complexity to the current regulatory framework. While such developments may hold great potential for optimal tailoring of treatments to diseases, they should not lead to unnecessary multiplication of rare diseases out of common diseases, neither of exclusivity periods.

The Orphan Regulation uses several incentives to make a previous neglected area more attractive to developers of orphan medicines. However, these incentives come at a cost. The costs to the Member States' health systems for reimbursing orphan medicines between

2000 and 2017 totalled about €20-25 billion; in addition to the EU and national public funding invested in research.

On the other hand, thanks to orphan medicines, patients gained 210,000 to 440,000 quality-adjusted life years, which constitutes a substantial improvement in the quality of life of patients with rare diseases in the EU. Furthermore, as the costs and benefits are based on an assessment of the 2000-2017 period, it seems quite likely that lower costs and/or higher availability of treatments for patients will apply in the longer term, as more generics and biosimilars will enter the market once existing products' orphan status expires.

The evaluation gives a nuanced picture of the effectiveness of the incentives provided by the Regulation. Developers of orphan medicines, particularly SMEs, have benefited from scientific advice that seems to have improved the possible success rate of a development. The overall share of SMEs has risen so much that they now account for half of requests for orphan designation. However, SMEs may not necessarily bring orphan medicines to the market themselves, as promising medicines are often acquired by larger pharmaceutical companies at a late stage of development.

One of the shortcomings that has been identified is that research institutes and academia cannot benefit from the fee waiver for which the Regulation provides, as it is reserved for SMEs.

As regards the Regulation's design, market exclusivity is the main incentive it provides. While the evaluation provides no evidence that might cast doubt on the market exclusivity concept as such, it exemplifies the weaknesses of a one-size-fits-all incentive.

The findings of the evaluation suggest that for the 73% of orphan medicines the market exclusivity reward has helped to increase profitability for these products, without overcompensating the sponsor. However, for the 14% of orphan medicines, the 10-year market exclusivity may have led to overcompensation. Hence the 10-year exclusivity is thus not fully justified for certain orphan medicines. These are often well-established use products, or medicines authorised for multiple orphan conditions.

Low turnovers do not necessarily signify an 'insufficient' return on investment for orphan medicines, as this depends on the specific situation: it is important to take account of development costs and whether there is any generic competition after the expiry of any protection for a given product. Without any precise data on development costs, it was difficult to estimate what would constitute an appropriate reward for the reduced return on investment of an orphan medicine. Nor is it easy to estimate the level of return of investment above which no reward is needed.

The real effect of market exclusivity was calculated to be an additional protection period averaging 3.4 years (in addition to the protection provided by patents/SPCs). The corresponding value of this reward was estimated at 30% of revenues from sales of orphan

medicines. The cost-benefit analysis for the pharmaceutical industry due to the Regulation has been positive.

Generic competition, according to the evaluation study, has only been observed for very few products to date. As market protection incentives will only expire in the coming years for several authorised orphan medicines, it seems likely that there will be increased generic entry from that moment. For orphan medicines, however, the literature suggests a slower price fall upon generic entry in comparison to other medicines. Among other factors, this may be because an *application* for a generic of an can be submitted i.e. only on the day the exclusivity period of the orphan medicine expires.

While the Regulation includes a mechanism to reduce the exclusivity period if a product is deemed to be profitable, the conditions under which the market exclusivity can be reduced to six years ex post are difficult to apply and rarely used. This finding goes hand-in-hand with the fact that only one application has been received under the 'insufficient return on investment' criterion, and that was subsequently withdrawn. This has shown that it is hard to estimate future investments and the returns on them in advance, before the therapeutic indications for which the product may be used have been established, and before the price at which it is to be sold is clear.

In recent years, it has been suggested that the 'insufficient return on investment criterion' could be used by developers in the field of novel antimicrobials. However, so far it has failed to attract companies, despite the unmet need and the clear market failure in this area.

The Regulation's potential inefficiencies and undesirable consequences were identified in certain cases. There are 22 orphan products authorised for two or more orphan indications, each referring to distinct orphan conditions, which are entitled to multiple periods of market exclusivity ('indication stacking'). Although it is desirable to broaden the therapeutic areas for which an orphan medicine can be used and this should be encouraged to serve patients in need. However, it is often unclear whether the additional market exclusivity period was needed to recover the additional costs of R&D. Additional orphan indications have been also identified as a barrier to developing generic orphan medicines. However, the overall 'inefficiency' is limited as the number of products authorised for multiple orphan indications in the EU is relatively small, and in most cases there is a very big overlap in the periods of market exclusivity for each indication. Finally, indication stacking should be seen in the light of advances in personalised medicine.

Medicines that were n well-established use as a magistral or officinal formula before their authorisation as orphan medicines, or which are repurposed established medicines, account for 19% of orphan medicinesin the EU. This is a lower figure than in the US. However, recent cases in which producers substantially increased the price of a newly-authorised orphan medicine that was already available to patients as a magistral or officinal formula, at a much lower price, have raised questions about this authorisation route. These price

increases seem to bear no relation to actual R&D costs.. Although price setting lies beyond the remit of the orphan Regulation, additional market exclusivity seems to be the main factor influencing monopolistic price setting in these cases. Consideration should therefore be given to the possibility of the Regulation's providing differentiated incentives, depending on the type of application for marketing authorisation or the level of investment in R&D.

There may be room for simplification and streamlining of internal processes including different scientific committees within the European Medicines Agency to avoid the risk of inconsistencies and delays in some cases. Furthermore, some procedures create additional administrative burdens and it should be considered if they are still necessary and proportionate (e.g. the obligation for sponsors to submit an annual report on the orphan designation to the Agency).

The instruments for which the legislation provides have been supported by a variety of EU initiatives and programmes, such as collaborative research and innovation projects, all aiming to boost the development of treatments for rare diseases. In addition, Member States have funded national programmes to support patient care and research into rare diseases. Despite this remarkable financial effort, the information available does not allow a direct link to be made between the publicly funded research projects on rare diseases and the orphan medicines actually developed. The reason for this is that the Regulation and the specific research programmes lack monitoring arrangements.

It is worth pointing out here that the Regulation is only one element in a set of measures designed to improve the situation of patients with rare diseases. The timely diagnosis of a rare disease or the availability of expert centres in the EU, which are now supported by the European Reference Networks, are other examples. Although important, the Orphan Regulation is only one piece in this puzzle.

Finally, the tools provide by the Regulation to ensure that patients suffering from rare conditions have the same quality of treatment as any other patient have only proven partially effective. While the *availability* of orphan medicines has increased under the Regulation, their *accessibility* varies considerably across Member States, mainly owing to factors beyond the Regulation (such as strategic launch decisions made by marketing authorisation holders, national pricing policies and the characteristic of reimbursement systems). The Regulation does not impose any obligation to marketing authorisation holders to market an authorised orphan medicine in all Member States. Nor does it contain any provisions on such matters as transparency of R&D costs or return on investment, to facilitate downstream decisions that would influence the affordability and accessibility of orphan medicines.

The Paediatric Regulation

As regards the Paediatric Regulation, the main innovation to improve the landscape was the introduction of a legal obligation for all new medicines under development.

This has resulted in an increase of almost 50% in clinical trials including children and in over 1000 paediatric investigation plans (PIPs) agreed. While most PIPs are still ongoing, given the long development time of medicinal products, the number of PIPs completed is gradually increasing, and 60% of all PIPs have been completed in the last three years.

The number of paediatric products authorised has also increased after the adoption of the Regulation. By 2016, 101 paediatric medicines and 99 new paediatric indications had been centrally authorised. In the same period, 10 new paediatric medicines received a national authorisation and 57 new paediatric indications were added to nationally authorised products.

In addition, the submission and analysis of clinical data already available before the Regulation took effect have enabled information on use in children to be added to almost 200 medicines. This means that these medicines can now be used more safely to benefit children.

These results are consistent with the impact assessment, which predicted that it would take 10 to 15 years for all patent-protected medicines (unless specifically exempted) to be specifically tested for children, and up to 20 years for most medicines to be authorised for paediatric use.

In contrast to these positive results, the evaluation also found that new paediatric products such as orphan drugs are not being developed in the therapeutic areas where needs are greatest. The Regulation has no effective instrument for channelling R&D into specific therapeutic areas. Development has been boosted mainly in areas where adult development was already planned. It thus looks as if the Regulation works best in areas where the needs of adult and paediatric patients overlap. However, major therapeutic advances have mostly failed to materialise for diseases that are rare and/or unique to children, and which often receive equal amounts of support under the orphan legislation. The existing design of the obligations laid down in the legislation may not be up to the task of capturing all adult developments that could potentially benefit children. For example, medicines are increasingly studied on the basis of their mechanism of action. The mechanism of action of a product developed to treat an ‘adult-only’ disease could also be helpful in treating a different disease in children. However, the Regulation exempts products for adult-only diseases from the obligation of designing a PIP. Another example concerns innovative clinical trial design, which may face difficulties with fitting in with the way PIPs are currently designed and agreed.

Moreover, the existing design of the rewards may not be such as to support the prioritisation of product development in areas of specifically paediatric need. This is true of the main reward the Regulation offers: the possibility of obtaining a six-month extension of the supplementary protection certificate (SPC) to offset the cost of conducting the mandatory clinical studies in children. This reward has not proven effective in encouraging industry to develop medicines in line with children's most pressing needs, where these differ from the needs of adults. Economically speaking, it actually brings far greater benefits for products with larger sales volumes. Most such products are medicines developed for use in adults as well as children.

The other major rewards provided by the Regulation, the additional two years of market exclusivity (the 'orphan reward') and the paediatric use marketing authorisation, PUMA, have rarely been used. They have thus done little to boost development in areas of unmet paediatric needs. The orphan reward, which cannot be granted in addition to the six-month extension of the SPC, is considered less valuable by developers than the SPC extension. Consequently, developers prefer to seek an SPC extension whenever possible.

The PUMA scheme, designed to channel EU research funds into boosting the development of new paediatric indications in off-patent medicines, has yielded disappointing results so far. However, about 20 PUMA-related PIPs are currently under way, so outcomes may improve in the next few years. Factors beyond the Regulation are the main reasons for the PUMA scheme's failure to yield more than a limited number of products. One example is the difficulty of obtaining higher prices than those applicable to the existing product, to cover the cost of new clinical research. Another is the difficulty encountered in conducting paediatric clinical trials of old products that are already available on the market and often widely used off-label. This outcome did not come as a surprise; the impact assessment had already predicted it as a possible scenario.

The Regulation includes some instruments to ensure that a paediatric medicine is placed on all EU markets once its PIP is completed and it has been authorised. Yet accessibility of paediatric medicines on EU markets can still be problematic. Their launch in the various EU markets is closely linked to the launch of the adult equivalent. This results in what are known as 'staggered roll-outs'.

In economic terms, the cost-benefit analysis conducted reveals a balance that is positive for both industry and society if one weighs up all the Regulation's impacts, both direct and indirect. This shows that combining obligations and rewards is an appropriate way to boost the development of children's medicines. However, the use of rewards was limited to 55% of the potentially eligible PIPs completed. At the same time, the SPC extension resulted in over-compensation in some cases and under-compensation in others. These facts indicate that the current system has certain limitations.

There have been comments from industry that the SPC system, regulated by a separate EU legislative act, is complex. Companies have to apply independently for SPCs (and for extensions) to patent offices in each Member State, which grant them independently. The SPC legislation is currently undergoing evaluation. While any modernisation or recalibration may address some of the inefficiencies identified, it could also directly affect the functioning of the paediatric reward system and thereby the Regulation itself. This shows the risks of using an 'external' legal instrument to provide the main reward available under the Regulation.

The legislation itself is perceived as burdensome by industry because it requires companies to establish the paediatric research plan – including the design of the paediatric trials – with the Agency at an early stage of development. At those early stages, however, overall product development may be subject to considerable change, requiring changes to the PIP as a result. This means the companies concerned have to submit requests for modifications to the Agency. This is particularly problematic in the case of an innovative trial design, where development plans are often shaped by the results obtained in previous phases of clinical development. Developers also see the national authorisation of paediatric trials as potentially burdensome, since it may in certain cases contradict what has already been agreed on in a PIP.

These aspects can be expected to improve with the application of the new Regulation on clinical trials, which will better harmonise the conduct of multinational trials and the implementation of the ongoing joint Agency-Commission paediatric action plan, which explores possible ways to improve the PIP procedure.

Outlook

When the Regulations were designed, the main priority was to increase the number of products for patients with rare and paediatric diseases in the EU. The Regulations met these objectives. However, expectations have developed further. It is recognised that the marketing authorisation stage is an interim step which does not necessarily mean that a given product is available across the EU, let alone that it is affordable for national health systems. Moreover, even within the small area of orphan and paediatric diseases, needs differ or change over time. Clustering of products is observable in some areas, while in others R&D is wholly absent, leaving high unmet needs. The Regulations have no tools to boost development in specific therapeutic areas of orphan and paediatric medicines. Scientific leads, market forces and expectations regarding revenues continue to exercise a strong influence on investment decisions.

From the outset, the two Regulations were never intended to be isolated measures to address the challenges identified. They were added to existing instruments, such as research funding and other policy tools, which could not on their own fully compensate for companies' lack of interest in investing in this area.

Accordingly, this means that the effects of the Paediatric Regulation cannot be viewed in isolation. Although it is an enabler, its objectives need to be aligned with *other* policies in order to create a seamless ecosystem from R&D to marketing. Any future adaptations would need to take all stages of public intervention into account. They would also need to take account of where public intervention is most effective and ensure that different interventions complement one another. Such an approach is necessary to prevent market-driven considerations from dominating this priority area.

Publicly funded research is important in this regard. However, not enough information was available to show whether public funding for research programmes had produced new orphan medicines for unmet medical needs, let alone whether they were available and readily accessible to patients across the EU.

While the two Regulations had appropriate objectives in terms of tackling market failure, the instruments chosen have had some unintended effects and created inefficiencies which need to be corrected. For example, orphan designations are sometimes granted on the basis of the prevalence criterion to products that have high returns on investment.

Moreover, some scientific developments could challenge established concepts used in both Regulations. Current legal definitions, used in both instruments, are directly linked to the concept of a disease and, for orphan medicines, to the prevalence of the condition. These legal provisions require amendment to ensure that the Regulations accommodate new scientific developments.

Finally, new issues such as unequal access and affordability create tensions and call for action. However, the Regulations can only go so far in addressing such issues, which are largely dependent on *external* factors.

Any future response to the shortcomings and future challenges identified in this evaluation should strike a balance between incentives for innovation on the one hand, and availability and patient access (for orphan and paediatric patients) on the other. These aspects are closely linked with the key objectives of the Pharmaceutical Strategy for Europe, of which orphan and paediatric legislation is part. The purpose of the Strategy is to create a future-proof regulatory framework through a wide-ranging examination of the pharmaceutical sector. Any changes to the orphan and paediatric framework will need to demonstrate that it contributes to these goals. Such changes should encourage investment in research and technologies that will actually reach patients and meet their therapeutic needs, while addressing market failures.