

# Revision of the EU legislation on medicines for children and rare diseases

## SUMMARY

On 26 April 2023, the European Commission launched a revision of the EU's pharmaceutical legislation, including legislation on medicines for children and for rare diseases. Since the early 2000s, the EU legislative framework has provided a complex set of obligations, incentives and rewards to stimulate the development of medicines for children and for rare disease patients. Over the last 20 years, the EU legislation has led to the development of new medicines for these categories of patients. The legislation has not been flexible enough, however, to integrate scientific and technological advances, nor has it been able to direct research and development towards areas of unmet medical needs.

Given the key role of Member States in determining the availability and affordability of medicines, implementation of the legislation cannot be assessed in isolation from the national context. This concerns, notably, key aspects such as pricing and reimbursement of medicines, taxation, and healthcare organisation, but also strategic decisions by pharmaceutical companies.

## Background

In the EU context, diseases are considered [rare](#) when they affect no more than five people per 10 000. Approximately 80% of rare diseases are of genetic origin, are often chronic and life-threatening, and the majority begin in childhood. Prior to the adoption of EU-wide legislation in the early 2000s, children generally received medicines indicated for use by adults and not tested for use in young patients. These medicines were likely to be inefficient or to present adverse reactions in children. Medicines for children were prescribed based on doctors' experiences ('off label use') rather than following clinical research. Clinical trials were often not conducted on this demographic due to the perception that children needed to be protected. Moreover, companies had limited interest in developing medicines for rare diseases, as it was not deemed profitable given the small number of patients and the high likelihood that the development costs could not be recovered.

To tackle these issues, in 2000 the EU adopted legislation on rare diseases, [Regulation \(EC\) No 141/2000](#) (Orphan Regulation). In 2006, it adopted [Regulation \(EC\) No 1901/2006](#) on medicines for children (Paediatric Regulation). Both regulations introduced a mixture of obligations, incentives and rewards to stimulate the development of new medicines. Their objectives partly overlap, as the majority of rare diseases may appear already in childhood and many children's diseases are also rare.

In 2020, the European Commission published a [joint evaluation](#) of the two regulations.<sup>1</sup> The evaluation showed that the legislation had stimulated research into and development of paediatric medicines and medicines treating rare diseases. However, this research had not sufficiently targeted areas of unmet medical needs, and [95% of rare diseases](#) still do not benefit from any form of treatment option to this day. Moreover, the authorisation of new treatments had not translated into



their availability across all EU Member States. The regulations have not been flexible enough to integrate technological and scientific advances such as the emergence of advanced therapies, use of [biomarkers](#) in the discovery of medicines or the use of innovative clinical trial designs.

## Main provisions in the Orphan and Paediatric Regulations

The **specific objectives of the Orphan Regulation** are i) to reward research and development through incentives and lead to new medicines for rare diseases, and ii) to ensure that patients suffering from rare diseases have the same quality of treatment as all other patients. Medicines that fulfil certain criteria are assigned an 'orphan designation', based on which they benefit from market exclusivity and other incentives. These criteria are: 1) **prevalence criteria** (no more than five people affected per 10 000) **or insufficient return upon investment criteria**; and 2) the condition is life-threatening or chronically debilitating. For the first criteria, it is considered that, without incentives, it is unlikely that the product would generate sufficient return to justify the investment.

The European Commission can grant a product the orphan designation based on a positive opinion by the European Medicines Agency (Agency), at any stage in its development. Once the development is complete, the product can be granted an EU-wide marketing authorisation. An EU-wide authorisation procedure is [compulsory for certain groups of medicines](#) but optional for others; however, the majority of innovative medicines must apply for an EU-wide authorisation. If all criteria are complied with, the product will enjoy **market exclusivity for 10 years** (up to 12 years if a paediatric research and development programme is completed). If, however, the product no longer meets the criteria for orphan designation after 5 years, the market exclusivity is shortened to 6 years.

The aim of the **Paediatric Regulation** is to compel pharmaceutical companies already developing medicines for adults to also screen them for possible use in children. The **specific objectives** are to: 1) ensure high quality clinical research in children; 2) ensure that most medicines used by children are specific for such use, with age-appropriate forms and formulations, while also ensuring their availability; and 3) increase availability of high-quality information about medicines for use in children.

At an early stage of development, companies are required to agree with the Agency on a paediatric research and development programme (**paediatric investigation plan (PIP)**) or to obtain a derogation (waiver) from it. On average, a PIP includes around three clinical studies. Compliance with these rules is checked when companies apply for marketing authorisation; in the event of non-compliance, the application is rejected for use in both adults and children. If a PIP is completed, the company may benefit from one of the two rewards:

- 1 **a 6-month extension** of the [supplementary protection certificate](#)<sup>2</sup> (SPC, extension of patent rights) which covers the entire product, not only the paediatric part;

or

- 2 **a 2-year extension of the orphan market exclusivity** for orphan medicines, which applies even if the product is deemed unsuitable for paediatric use.

Moreover, a **paediatric-use marketing authorisation (PUMA)** has also been in place to facilitate development of paediatric indications for existing authorised products no longer covered by a patent or an SPC. It is an **8-year period of data protection**, which runs in parallel with the 10-year market protection period. This aims to protect the new product from immediate competition with generic medicines already on the market.

The evaluation covered the implementation of both regulations. The assessment covers the 2000-2017 period for the Orphan Regulation and the 2007-2017 period for the Paediatric Regulation; no impact assessment had been carried out on the Orphan Regulation, with desk research used as the baseline for comparison. Prior to 2000, 15 medicinal products<sup>3</sup> for rare diseases were authorised at EU level; 70 products authorised in the US were also available in the EU (known as 'orphan-likes'). The baseline used for the Paediatric Regulation is a prior impact assessment.

## EU-level reports and evaluations

### Evaluation of the Orphan and Paediatric Regulations

#### Effectiveness of the Orphan Regulation

The Commission evaluation highlighted the fact that the **Orphan Regulation** had contributed to the development of **new treatments for rare diseases**. Out of 142 orphan medicines authorised since 2000, 18 to 24 medicines were developed as a result of the incentives provided under the legislation. However, the regulation was not able to catalyse clinical development towards areas where no treatments existed. Regarding the orphan medicine designation, the criterion of 'insufficient return on investment' had only been used once, as sponsors feared being reassessed after 5 years of market exclusivity. However, access to new treatments varied significantly across the Member States, mainly due to factors beyond the remit of the regulation, such as reimbursement systems, company strategies on market launches and the role of healthcare providers.

After the first 5 years of implementation, 22 orphan medicines had been authorised for 20 different rare diseases. By 2017, **142 orphan medicines**<sup>4</sup> were authorised on the EU market. Based on the assessment in the evaluation, since 2011 the number of marketing authorisations for orphan medicines had grown faster than that for non-orphan medicines.<sup>5</sup> As mentioned above, it could be estimated that 18-24 orphan medicines were directly attributable to the regulation. However, the Commission cautioned that, due to the lack of sufficient data, the figures were indicative and potentially under-representative.

While the Orphan Regulation was designed to address **patients' unmet medical needs**, the evaluation has shown that the regulation has gradually become less effective in directing research to areas with no available treatments. While in 2001 78 % of orphan designations were for new indications, in recent years this figure has declined to 20 %. This could be attributed to a variety of factors, including the fact that pharmaceutical companies tend to focus on certain areas of disease, a lack of scientific expertise or a lack of basic research in certain fields. However, anti-cancer treatments account for a third of all designations, given that treatments for rare cancers have broader applicability across a range of cancers, and are therefore more likely to be profitable.

#### Terminology

**Marketing authorisation application:** An application made to a European regulatory authority for approval to market a medicine within the EU.

**Market protection:** Period of protection during which generics cannot be placed on the market.

**Sponsor:** Legal entity responsible for submitting an application for orphan designation to the EU.

**Generic medicine:** Contains the same active substance(s) as the reference medicine. The generic is marketed after expiry of the data and market protection.

**Biological medicine:** A medicine whose active substance is made/derived from a living organism such as living cells or organisms (human, animals and microorganisms such as bacteria or yeast).

**Biosimilar:** A biosimilar is a biological medicine that is very similar to another biological medicine which has already been approved.

**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.

**Therapeutic indication:** A medical condition for which a medicine is used. This can include the treatment, prevention and diagnosis of a disease.

**Patent:** A legal title that can be granted for any invention having a technical character, provided that it is new, involves an 'inventive step', and is susceptible to industrial application.

**SPC:** Serves as an extension to a patent right. The aim is to offset the loss of patent protection for pharmaceutical products that occurs due to the lengthy testing and clinical trials required prior to obtaining regulatory marketing approval.

Source: [Joint evaluation](#) SWD(2020) 163, [European Commission](#).

Moreover, granting **market exclusivity** to a product may deter the development of follow-up products of an orphan indication covered by the first product. For 82 % of orphan indications where there is at least one authorised product, there is no other authorised product on the market. This situation can be explained by several factors that companies consider, such as the number of people affected by the disease, turnover of the first product, and availability of scientific knowledge. Long development times for medicines and market size also play a role in the decision to pursue the development of a new product.

The evaluation also examined whether the **prevalence threshold** – five people affected in 10 000 – was an appropriate criterion. The evaluation referred specifically to a [recent study](#)<sup>6</sup> showing that 84.5 % of analysed rare diseases had a very low prevalence (less than one person in a million). In this context, stakeholders indicated that the expected use of a product should be taken into account (once, repeated, life-long). Moreover, to target neglected therapeutic areas, incentives could be developed depending on the rarity of the disease or the scale of investment needed. For this purpose, the rare disease registries project supported by the [European reference networks \(ERNs\)](#) could be used as a reference. ERNs are virtual networks connecting healthcare professionals around Europe with expertise in rare diseases, allowing them to discuss a patient's diagnosis and care.

Regarding **availability of orphan medicines**, the evaluation showed that the regulation had helped make the medicines available faster and more widely across the EU. Prior to the authorisation of the 142 medicines, there was no satisfactory treatment available in the EU for eight out of 20 rare conditions. However, the authorisation of medicines at EU level does not guarantee that the medicines are made available in all Member States. Austria, France, Germany and Italy have a high market uptake of orphan medicines, suggesting that the market conditions there may be more favourable. The Orphan Regulation does not make it obligatory for a specific product to be made available across the entire EU; companies choose whether to launch a product in a country based on many factors such as the affected population, existing competition or alternative treatments.

Factors beyond the remit of the regulation have an impact on the availability of orphan medicines and their reimbursement, and **national pricing and reimbursement practices and policies** influence patients' access to orphan medicines. For instance, countries determine the 'maximum allowed reimbursable price based on the prices averaged over a set of fixed reference countries'.<sup>7</sup> This is known as an 'external reference price' and translates into companies placing a product on the market in some countries faster than in others. The evaluation shows<sup>8</sup> that companies tend to launch more medicinal products faster in wealthier countries with a higher gross domestic product (GDP) per capita than in countries with lower per capita GDP.

Moreover, health ministries lay down policies/criteria on how public funds are directed regarding pharmaceutical products. Their decisions are often supported by **health technology assessments** (HTAs); these measure the added value of a new health technology compared to existing ones on the market. The methods used for HTAs differ among Member States and their outcomes vary based on characteristics of national healthcare systems and the way in which treatments are carried out. Decision-making on reimbursements is influenced by the work of HTA agencies and the cost-benefit analyses they conduct. Despite this evidence, the evaluation found<sup>9</sup> that, in most Member States, there were no major differences in reimbursements between orphan medicines and other medicines. Finally, the **role of healthcare practitioners, and specifically their prescription practices**, is crucial. The practitioners may not prescribe the medicine immediately either due to insufficient knowledge of: i) the rare disease; or ii) the potential benefits and availability of the new medicine.

## Effectiveness of the Paediatric Regulation

The Commission acknowledged that the **Paediatric Regulation** had led to an increase in clinical research and medicines for children, although it noted that this was particularly the case when adult medicines were developed in parallel. In addition, the regulation had led to a reduction in the use of off-label adult medicines in children. However, the regulation was not able to direct research and

development toward therapeutic areas aimed at developing remedies for rare diseases in children. Little use was made of the PUMA reward or the 2-year market exclusivity for orphan medicines, but the SPC 6-month extension was considered especially 'relevant' in the case of products with high sales for adults.

The evaluation found that **over 1 000 PIPs** had been agreed by the end of 2018.<sup>10</sup> Paediatric clinical trials increased from 188 to 473 in the 2007-2016 period, over 60% of which had been completed in the 2013-2016 period. By 2016, 101 paediatric medicines had been authorised; compared to the 2004-2006 period, the output of new paediatric medicines had increased considerably (30 medicines at the time).

At the same time, the Commission noted that, by the end of 2017, the Agency had approved **almost 500 waivers** from the obligation to conduct a PIP (against the agreed 1 000 PIPs). Article 11 of the Paediatric Regulation allows the waiving of the obligation to conduct a PIP if the disease does not exist in children. However, in the case of cancers, certain compounds could still be useful in children for other conditions. This situation eventually led to a review of the waiver rules in 2015.<sup>11</sup> Moreover, in the context of a PIP, studies on adults should be conducted prior to initiating studies on the paediatric population or in cases where the studies on the paediatric population would take longer. However, in practice, this has led to a deferral of neonatal studies, leaving this age group exposed to inadequate treatments.

Once a PIP has been completed, a product can **benefit from an SPC**; however, some companies fail to finalise them on time. An SPC should be requested 2 years before the 10-year protection period expires. SPCs extend patent rights to protect innovation and compensate for lengthy clinical trials and marketing authorisation procedures; by 2016, over 40 products had benefited from this additional protection. It is worth noting that the SPC applies to the whole product, so it is interesting for those products that generate the highest return on investment, and not necessarily for those with the greatest paediatric need.<sup>12</sup> Moreover, the completion of a PIP does not guarantee that the SPC is granted automatically. The SPC is only given if:

- 1 a product has been authorised in all Member States;
- 2 if a paediatric indication is authorised for an existing product, in which case it has to be placed on the market within 2 years;
- 3 if an authorisation holder discontinues the marketing of a product, in which case they must transfer the authorisation to another or provide access to the data.

Regarding the **PUMA reward (8 years of data protection)**, the Commission concluded that the scheme had not been as successful as the SPC. While the former extends protection only for the indications covered by the orphan designation, the latter extends protection for all the indications of a product. By 2018, only six paediatric medicines had used the PUMA scheme. The main factors explaining this low number are:

- 1 the products concerned were already on the market and both health professionals and patients were not motivated to engage in studies;
- 2 Member States placed less value on older medicines and were not willing to pay a higher price to cover the development of a paediatric formulation.

When averaged over the medicines analysed in the evaluation, including products without any primary patent or SPC protection at the start of the market exclusivity period, the **average additional protection** offered by the **market exclusivity amounted to 3.4 years**.<sup>13</sup> In other words, the product was protected from competition for an **additional 3.4 years** on top of the protection provided by patents/SPCs. The 3.4 years translate into an economic value of 30% of total turnover, as calculated against the set of medicines analysed in the evaluation.

As detailed in [Annex 3](#) of the evaluation, protection offered by market exclusivity differs from that offered by patents/SPCs. Whereas the latter protect only against products with the same active

substance and for the same indication (generic or biosimilar products<sup>14</sup>), **market exclusivity protects more broadly against all products that are considered 'similar'**. Should a sponsor develop a product that is similar to an existing orphan medicine, they would have to demonstrate that their product has a 'significant benefit' in order to be granted market authorisation.

Alongside market exclusivity, the **orphan medicine designation** has also led to companies deciding to launch products on the EU market. Based on an orphan designation, a company can ask for **protocol assistance** (scientific advice from the Agency) on conducting the tests and clinical trials necessary to demonstrate the quality, safety and efficacy of their product; there were more than 125 requests for protocol assistance in 2017. Orphan designation also allows sponsors to benefit from **waivers from fees** associated with the marketing authorisation procedure. This can be useful for charitable foundations and academic institutions, as the fees can be significant. Lastly, Member States also provide support, including through tax incentives.<sup>15</sup>

## Efficiency of the Orphan Regulation

Regarding **costs of development** of orphan medicines by the pharmaceutical industry, the Commission provides estimates in the evaluation, as most companies were unwilling to share information on their R&D costs. As such, based on figures in available literature, the costs of development of an orphan medicine range from €479 million to €725 million. Assumptions on R&D costs were made for the development of 21 products attributed to the regulation in the 2000-2017 period (see Section 2.1. in Annex 3 of the evaluation); these costs amounted to €11 billion. The costs of manufacturing, marketing, distribution and applicable taxes were estimated at €12.04 billion.

The most obvious **benefit** of the Orphan Regulation has been that orphan medicines enter the EU/EEA market faster and are more widely available. The estimated value of sales of orphan medicines in the 2000-2017 period was €19.11 billion, the additional 3.4 years of protection compensated for R&D costs worth €4.59 billion, and a further €0.16 billion was estimated as having been gained from fee waivers and protocol assistance. The available data did not allow for the calculation of the total net benefit to industry; however, based on assumptions, the evaluation estimated a net benefit of €0.82 billion in the 2000-2017 period. It is expected that revenues and profits will continue to be generated from these products long after 2017.

The costs to the **healthcare sector** (e.g. treatment with orphan medicines) were estimated at €23.7 billion. The evaluation also assumed that public funding covered the majority of healthcare costs. Costs to **public authorities** attributable to the Orphan Regulation were estimated at €24.3 billion (e.g. healthcare financing of orphan medicines, research subsidies, number of staff).

The evaluation found that, for the 73 % of orphan medicines with an annual turnover below €50 million, the market exclusivity reward helped to increase profitability. However, for the 14 % of orphan medicines with an annual turnover above €100 million, the 10-year market exclusivity might have led to overcompensation.

Twenty-two orphan medicines on the EU market are authorised for two or more orphan indications, each with periods of market exclusivity running in parallel. In this context, the evaluation noted limited generic competition but with a smaller drop in price for the orphan medicines than for the non-orphan ones. However, limiting the 10-year market exclusivity period could be considered for each subsequent indication to avoid overcompensation, as suggested by various stakeholders.

## Efficiency of the Paediatric Regulation

The **annual costs<sup>16</sup> incurred by the pharmaceutical industry in relation to the implementation of the regulation** were estimated at €2 106 million. While €82 million are administrative costs, the rest essentially concern R&D. Average costs per PIP were estimated at €19.6 million, spanning several years, as the average length of a PIP ranges from 5 to 10 years (with some lasting up to 20 years). The economic value of benefiting from an SPC extension was also assessed, but this may vary across countries (e.g. national policies) and across products (e.g. competitiveness of a specific market). This

was calculated as a percentage of total revenue – for eight products in the evaluation – with an estimated average of 56.6% benefit to the company. The impact assessment had anticipated that an SPC extension could offset the costs incurred throughout a PIP.

By 2016, however, only 55% of completed PIPs had benefited from a reward. The economic value of the orphan reward was not assessed, as very few products benefited from it. The PUMA reward was considered too costly, as the new indication needed to be developed only for children. It also did not offer meaningful market exclusivity, as the product could still be subject to off-label use of generics. The annual costs incurred by **regulators**, including the Agency and the national agencies, matched the costs indicated in the impact assessment at €5 million.

It is worth noting that the award of the SPC extension is granted even if the outcome of a PIP is negative. This translates into costs for society and patients, as the entry of the generic medicine for adults is delayed and no new paediatric medicines are delivered. Moreover, companies can submit parallel authorisations worldwide for the same medicine, leading to duplication in research. To address this, since 2007 a monthly exchange among regulators takes place, including countries such as Australia, Canada, Japan and the US.<sup>17</sup> An Agency-Commission paediatric plan provides further improvements in this area, as explained below.

## Coherence

The **Orphan Regulation** was seen as offering a coherent set of incentives such as fee waivers, protocol assistance, market exclusivity and support for research. However, better alignment on procedures is needed among the four Agency committees dealing with both paediatric and orphan medicines.

Since 2000, more than €1.7 billion has been made available via the EU Framework Programmes for Research, Technological Development and Innovation to over 340 collaborative research and innovation consortia (projects) in the area of rare diseases.<sup>18</sup> With respect to measures taken at national level, it is worth noting that, in the 2009-2017 period, the number of Member States with national plans/strategies on rare disease research increased from four to 23. It was not possible to assess in the evaluation how EU research and national research complemented each other due to a lack of monitoring indicators. As such, it could not be determined to what extent public investments had contributed to successful authorisations of medicines.

The Orphan Regulation interacts with [Directive 2001/83/EC](#) on human medicinal products, the [SPC Regulation](#) (Regulation (EC) No 469/2009) and the [ATMP Regulation](#) (Regulation (EC) No 1394/2007) on advanced therapy medicinal products. Developers of orphan medicines can benefit from incentives and rewards under each of these instruments. However, under the Orphan Regulation they can only submit an application for marketing authorisation of generics **at the end** of the 10-year protection period; this delays the entry of the generic version onto the market. Developers of medicines under Directive 2001/83/EC can, for instance, submit applications earlier, prior to the expiry of the protection period.

The obligations and rewards under the **Paediatric Regulation** were seen as working in a coherent way. However, national rules on the conduct of trials can delay the completion of a PIP. In addition, the granting of an SPC remains within the remit of national patent offices, which was seen as an additional obstacle by the pharmaceutical companies.

The Paediatric Regulation interacts with the [SPC Regulation](#) and [Directive 2001/20/EC](#) on clinical trials.<sup>19</sup> As the SPC Regulation is [currently being revised](#), its modernisation will likely also have an impact on the rewards for paediatric medicines. Regarding clinical trials, divergences of an ethical nature were visible at national level on the conduct of trials in children; requests could also be made for delays in these trials until more data was made available in adults. More recently, the joint Agency-Commission paediatric action plan has provided certain measures to tackle these issues. The new [Clinical Trial Regulation](#), which replaces Directive 2001/20/EC, is expected to lead to a

harmonisation of the rules on conducting clinical trials. This should also make it easier for pharmaceutical companies to conduct multinational clinical trials.

## Relevance

In assessing the relevance of the two legislative acts, the evaluation noted that the problems identified in the early 2000s were still present today – specifically, a lack of treatment options for rare diseases and of medicines formulated for children. However, the lack of treatment options today extends well beyond rare diseases. New emerging diseases are regularly identified, at a rate of at least one or more per year since the 1970s. Infectious diseases are one class of diseases where treatments are lacking. In addition, certain antibiotics are no longer effective due to antimicrobial resistance.

The orphan medicine market has become more financially attractive,<sup>20</sup> with treatments covering some therapeutic areas while others still do not benefit from any treatments. New antimicrobials are not produced by pharmaceutical companies due to concerns about non-profitability, similar to the situation for rare diseases. While both legislative acts have led to the development of medicines targeting children, their provisions have not sufficiently influenced the availability (and affordability) of these medicines across the EU.

In recent years, [advanced therapy medicinal products](#) (ATMP) and [biological medicines](#) account for a growing proportion of all EU orphan designations. ATMPs are medicines that are based on genes, tissues or cells and may arrive on the market based on a [conditional marketing authorisation](#). Therefore, these medicines are authorised based on 'less comprehensive clinical data', allowing companies to provide more evidence at a later stage. This concerns areas where no treatments are available or for emergencies (e.g. a pandemic). However, the lack of sufficient data makes it difficult to assess whether these products do provide a significant benefit over existing ones and, in the end, whether the orphan designation can be granted.

Moreover, the [emergence of biomarkers](#) has also created a number of challenges. For instance, in a cancer patient the development of treatments can now be guided by the presence of specific biomarkers regardless of the tissue or origin of the cancer. This can lead to treatments covering multiple types of cancer; however, this may in turn require changes to the definition of the specific orphan condition to allow for the subsequent granting of the orphan designation.

Lastly, innovations in the conduct of clinical trials can also affect the way the two regulations are implemented. [Basket trials](#), for instance, provide evidence on the mechanism of action rather than the efficacy of a treatment. Basket trials can investigate multiple rare diseases simultaneously (e.g. shared genetic mutation) with a single treatment intervention. With small sample sizes and new mechanisms of action, in addition to the existing definition of the condition, it may be difficult for the Agency to conduct the authorisation procedure. In the case of such innovative trials, PIPs may need to be changed several times, creating additional costs and possibly delaying authorisation.

## EU added value

The Orphan Regulation marked the start of the development of an EU strategy to treat rare diseases. Between 2000 and 2017, 1 956 orphan designations were granted and 142 orphan medicines were authorised in the EU. The adoption of the regulation encouraged Member States to draw up national plans of their own, with 25 having done so by 2019. The regulation boosted the growth of the orphan medicines market, an objective that would have been difficult to achieve based solely on national initiatives.

The impact assessment of the Paediatric Regulation showed that, despite Member States having encouraged industry to develop paediatric medicines, their attempts had been largely unsuccessful. The regulation has led to an increase in the development of paediatric medicines since 2007, similar to the situation in the US following the introduction of comparable legislation in the 1990s.



## Revision of the EU pharmaceutical legislation

On 26 April 2023, the Commission put forward a 'pharmaceutical package' to revise the EU's pharmaceutical legislation and make medicines more available, accessible and affordable while supporting the competitiveness and attractiveness of the EU pharmaceutical industry, with higher environmental standards. The package includes [two legislative proposals](#), a new [directive](#) and a new [regulation](#), which replace the existing pharmaceutical legislation, including the legislation on medicines for rare diseases and children. The reform also includes a communication on the reform and a Council [recommendation](#) on antimicrobial resistance. Some of the main proposed changes are highlighted below.

The suggested approach is a shift away from a 'one-size-fits-all' system of incentives to a **modulated system of incentives** that rewards companies that fulfil important public health objectives. For **innovative** medicines, including **paediatric medicines**, the period of market exclusivity would be 8 years. Additional periods of protection can be obtained if the companies launch the medicine in all Member States (+ 2 years), if the medicine addresses an unmet medical need (+ 6 months), or if comparative clinical trials are conducted (+ 6 months). A further year of data protection could be granted if the medicine can treat other diseases. Therefore, the maximum period would be increased to 12 years, while today it is 11 years.

For **medicines for rare diseases**, the period of market exclusivity would be **9 years**. However, companies can benefit from additional periods of market exclusivity if they address a high unmet medical need (+ 1 year), launch the medicine in all Member States (+ 1 year), or develop new therapeutic indications for an already authorised orphan medicine (up to 2 extra years). Therefore, the maximum period would be increased to 13 years, while today it is 10 years. Transferable data exclusivity vouchers would be offered to developers of novel **antimicrobials**; the developers would benefit from an additional year of data protection from competition.

The revision will also aim to speed up the marketing authorisation procedures and facilitate faster entry onto the market of generics and biosimilars. Moreover, pharmaceutical companies would be required to publish information on all direct financial support received from any public authority or publicly funded body. Lastly, the revision will also address issues such as security of supply, shortage of medicines, and environmental protection.

## European Parliament resolutions/MEPs' written questions

### European Parliament resolutions

In its [resolution](#) of 31 May 2023 on combating antimicrobial resistance (AMR), the European Parliament called on Member States to put in place national action plans in line with the World Health Organisation Global Action Plan and the United Nations 2016 Declaration on AMR. It also called on Member States to close surveillance and monitoring gaps in data on both AMR and antimicrobial consumption (AMC) by 2030. It further recommended that the Commission establish an EU-level database of data on AMR and AMC in human health, animal health and the environment.

In its [resolution](#) of 24 November 2021 on the EU's pharmaceutical strategy, Parliament called on the Commission to assess the system of incentives to promote research into and development of medicines for unmet needs. It referred specifically to cancers, including paediatric cancers, rare diseases, neurodegenerative and mental illnesses and AMR. It also urged the Commission to promote the creation of an EU framework to guide and evaluate the implementation of national plans combating these illnesses. Regarding availability of authorised medicines, Parliament called on the Commission to consider policy options that would guarantee access to medicines in all Member States, following their authorisation at EU level. It further drew attention to the differences in validity of patents and SPCs across the Member States and called on the Commission to revise the use of SPCs to enable generic and biosimilar medicines to become more competitive within and outside the EU.

In its [resolution](#) of 10 July 2020 on a post-pandemic public health strategy, Parliament had called for an EU action plan on rare and neglected diseases. This request was also mentioned in subsequent parliamentary questions, for instance in [October 2021](#) and in [January 2022](#).

## Selected written questions

**Written question on [ensuring access to medicines](#) by Milan Brglez (Slovenia, S&D), 6 January 2023:** The Member inquired about upcoming tangible proposals to address shortages of medicines for rare diseases.

**Answer given by Stella Kyriakides on behalf of the European Commission:** The Commission clarified that the revision of the Orphan Regulation would focus on ensuring equal access to innovative medicines on the market. The continuous supply of medicines would be addressed as part of the revision of the general pharmaceutical legislation, which would aim to enhance security of supply and address shortages through stronger obligations. This could include obligations regarding supply and transparency, earlier notification of shortages and withdrawals, more transparency on available stocks, and stronger coordination and mechanisms at EU level.

**Written question on [paediatric research infrastructure](#) by Piernicola Pedicini (Italy, Greens/EFA), 1 February 2022:** The Member highlighted that basic research linked to different paediatric ages was needed, given that many paediatric pathologies were still without a treatment. The Member asked whether focused paediatric research infrastructure including preclinical/clinical research could be funded and implemented. In addition, the Member inquired whether the European reference networks could be extended to other vulnerable populations such as children.

**Answer given by Mariya Gabriel on behalf of the European Commission:** The Commission provided a range of information on both questions, of which a selection is mentioned here. For instance, paediatric research infrastructure is already included under the projects undertaken within the [European Strategy Forum on Research Infrastructures](#). Moreover, the [Paediatric Clinical Research Infrastructure Network](#) has developed a common infrastructure for paediatric trial management. Since 2017, ERNs cover rare and complex diseases and, in many cases, these cover child patients. Examples of such ERNs include [MetabERN](#) (metabolic diseases), [ERN-RITA](#) (paediatric rheumatology), [ERN TransplantChild](#) and [ERN PaedCan](#) (paediatric cancers).

**Written question on an [action plan for rare diseases](#) by several Members, 28 January 2022:** The Members stressed that sickle cell disease was the most prevalent genetic disease in Europe. In addition, they noted that the COVID-19 pandemic had exacerbated inequalities in access to healthcare. In this context, they inquired as to whether: i) universal new-born screening would be included in the revised Orphan Regulation; and ii) whether an action plan on rare diseases would be developed at EU level in 2023.

**Answer given by Stella Kyriakides on behalf of the European Commission:** While the Commission acknowledged that better criteria were needed to determine unmet needs of patients suffering from rare diseases, it considered that 'disease specific needs' could not be introduced in the upcoming legislation. It further recalled that, at EU level, action is taken based on a [Council recommendation](#) on action in the field of rare diseases issued on 8 June 2009. In addition, the Commission provided support to the existing 24 [European reference networks](#) on rare and low-prevalence complex diseases.

## Agency-Commission joint paediatric action plan

In 2017, the European Commission published a [10-year report](#) on the implementation of the Paediatric Regulation. The report showed that, while the regulation had led to an increase of medicines for children, their development still lagged behind that of adult medicines. In 2018, the Agency and the Commission therefore proposed an [action plan](#) to address the challenges identified in the report. Since then, actions have been taken in five streams: 1) Identifying paediatric medical needs; 2) Strengthening cooperation of decision-makers; 3) Ensuring timely completion of

paediatric investigation plans; 4) Improving the handling of PIP applications; and 5) Increasing transparency around paediatric medicines.

Many initiatives have been launched – as can be seen in the [annex to the report](#) – with some highlighted here. For instance, regarding collaboration on the **conduct of clinical trials**, the [European network of paediatric research](#) (Enpr-EMA) set up a working group in 2018 including regulators and research networks across six regions (Australia, Canada, the EU, Japan, the UK and the US). A framework was also developed for a '**stepwise PIP**' concept, an approach allowing changes to be made to a PIP as more evidence becomes available over time; the Agency launched a [pilot](#) in February 2023. Regarding the identification of paediatric medical needs, the Agency has organised [multi-stakeholder workshops](#) with a focus on specific diseases such as paediatric inflammatory bowel disease and atopic dermatitis.

Other initiatives include the [Innovative Medicines Initiative](#) projects such as [conect4children](#), a collaborative European network that aims to facilitate the development of drugs and therapies for the paediatric population. These exchanges and initiatives have enhanced the ability of the Agency to assess the potential of new products to tackle unmet therapeutic needs. Moreover, the Agency has also regularly discussed paediatric medicine development with international regulatory bodies via its [paediatric cluster](#).

## Other EU institutions and bodies

### Council of the European Union

In its June 2021 [conclusions](#) on access to medicines and medical devices, the Council acknowledged the importance of reaching a balance in terms of regulatory incentives to ensure the development of and access to innovative medicinal products, but also of generics and biosimilars and 'older' medicinal products. It also noted the impact of rising prices, increasingly complex therapies and health emergencies on ensuring affordable health systems. In this context, it recognised the need for a comprehensive horizon scanning to inform the Member States in anticipating challenges and developing strategies at national and EU level (e.g. when dealing with high-cost emergent technologies). It took note of the [International Horizon Scanning Initiative](#), which aims to empower decision-makers and organisations to drive informed pricing decisions for medicinal products. Moreover, the Council noted that Member States did not share a commonly agreed understanding of 'unmet medical needs' (UMN). It therefore invited the Member States and the Commission to discuss a 'set of commonly accepted criteria for UMN' applicable to orphan and paediatric medicinal products, medical devices and in vitro diagnostic medical devices. Regarding access and affordability of innovative products, the Council highlighted the need for an exchange of ideas on payment mechanisms, particularly with respect to UMNs and those aimed at specific populations, including older medicines.

### European Economic and Social Committee

In an October 2022 [opinion](#), on solidarity for rare disease patients, the European Economic and Social Committee (EESC) calls for a comprehensive European action plan on rare diseases with SMART goals attainable by 2030, to ensure that all rare disease patients enjoy equal opportunities for diagnosis and treatment. It further suggests extending the Health Emergency Preparedness and Response Authority (HERA) mandate or using it as a model to create a new European authority for non-communicable diseases. In its view, this would foster cooperation and solidarity regarding rare diseases to help coordinate the implementation of a European action plan on rare diseases and to ensure a European approach to non-communicable rare diseases. The EESC believes that optimal use should be made of the ERNs and calls for their integration into the EU and national healthcare systems. In the meantime, several issues should be addressed, notably: the lack of reimbursement for healthcare providers in the ERNs but also for virtual consultations, and administrative and technical interoperability issues.

## ENDNOTES

- <sup>1</sup> See also [annexes](#) to the evaluation: [part 2](#), [part 3](#), [part 4](#), [part 5](#), [part 6](#).
- <sup>2</sup> The SPC system is codified in [Regulation \(EC\) No 469/2009](#).
- <sup>3</sup> Five of these 15 products belonged to the group of 'immunomodulating agents', three addressed diseases of the blood and blood-forming organs like leukaemia, and another three addressed diseases of the alimentary tract and metabolism. The rest addressed diseases of the genito-urinary system and the nervous system.
- <sup>4</sup> Between 2000 and 2017, 1 956 designations were granted and 142 orphan medicines were authorised (11 were subsequently withdrawn, thus leaving 131 on the market).
- <sup>5</sup> See [Annex 3](#) to the evaluation ([SWD\(2020\) 163](#)), Section 1.4.2.
- <sup>6</sup> Nguengang Wakap S., Lambert D., 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.
- <sup>7</sup> Section 6.2.2 of the [Study to support the evaluation of the EU Orphan Regulation](#), European Commission, 2019.
- <sup>8</sup> Section 2.2 of the [Study on the economic impact of the supplementary protection certificates, pharmaceutical incentives and rewards in Europe](#), European Commission, 2018.
- <sup>9</sup> Section 6.2.2 of the [Study to support the evaluation of the EU Orphan Regulation](#), European Commission, 2019.
- <sup>10</sup> See Section 3 in [10 years of the EU paediatric regulation](#), European Commission, 2017, and [annual reports from the Agency](#).
- <sup>11</sup> The Agency tried to mitigate this issue through a review of its class waiver decision in 2015, revoking some automatic waivers for carcinomas. See the European Medicines Agency's [revision of the class waiver list](#) on 23 July 2015.
- <sup>12</sup> See the [Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe](#), Chapter 5, European Commission, 2018.
- <sup>13</sup> See [Annex 3](#) to the evaluation ([SWD\(2020\) 163](#)), Section 1.4.2.
- <sup>14</sup> See also [Commission Regulation \(EU\) 2018/781](#) of 29 May 2018 amending Regulation (EC) No 847/2000 as regards the definition of the concept 'similar medicinal product'.
- <sup>15</sup> Inventory of Union and Member State incentives to support research into, and the development and availability of, orphan medicinal products ([SWD\(2015\) 13](#)).
- <sup>16</sup> See Section 2.2 of the [Study on the economic impact of the Paediatric Regulation, including its rewards and incentives](#) European Commission, December 2016.
- <sup>17</sup> The [Agency-Commission joint paediatric action plan](#) provides for further improvements in international cooperation.
- <sup>18</sup> FP5, FP6, FP7 and Horizon 2020. For more up-to-date information, see the Commission [website](#) on rare diseases.
- <sup>19</sup> [Regulation \(EC\) No 536/2014](#) on clinical trials will replace this directive. Although it entered into force on 16 June 2014, the timing of its application depends on the development of a functional EU clinical trials portal and database.
- <sup>20</sup> Section 6.4 of the Orphan study report (2019).

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