



Study to support the evaluation of the EU Orphan Regulation

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Abstract

Background

To support the development of new medicines for the treatment of rare diseases and to promote greater access to such treatments in the EU, in 2000 the EU Orphan Regulation was introduced. The Regulation foresees in a set of incentives and regulatory rewards for developers ('sponsors'), aimed at addressing issues underpinning market failures in this area.

Objectives

This study reviews the objectives and design of the Regulation and assesses to what extent it has proven effective, efficient, and relevant (2000-2017). Additionally, it examines the internal coherence between the Regulation at the level of the EU, as well as external coherence with national policies and initiatives in EU Member States. The EU added value of the Regulation has also been reviewed. A discussion of achievements, as well as of shortcomings and challenges is also provided.

Methods

The study draws upon existing data sets as well as the collection of new data. A comprehensive analysis was performed of available literature and of data provided by the European Medicines Agency. A targeted consultation, using surveys and interviews, was performed under 5 distinct groups of stakeholders: 1) representatives of national public authorities in EU Member States, 2) sponsors of orphan medicinal products, 3) developers of generic medicines, 4) patient and consumer organisations, and 5) academic researchers and experts. Additionally, IQVIA sales data and additional secondary sources were used to estimate the costs associated with the Regulation and to conduct a high-level cost-assessment.

Findings

The EU Orphan Regulation has made important contributions to overall development of new orphan medicines, both by improving the R&D climate and by providing economic incentives to sponsors. It has also catered for faster time to market for new medicines and to increased access at the level of the EU. At the same time, substantial challenges remain in addressing unmet medical needs, including for children. Sectoral and scientific developments are also posing challenges to the current regulatory framework, necessitating a critical review.

Key words: Orphan Regulation, orphan medicines, paediatric medicines, rare diseases.

Executive Summary

Study objectives

This study supports a comprehensive joint evaluation of the EU Orphan Regulation and the EU Paediatric Regulation. This study has hereto gathered information on five evaluation dimensions: A) relevance, B) effectiveness, C) efficiency, D) coherence and E) EU added value of the EU Orphan Regulation. The goal was to gather and analyse factual information on the outcomes and impacts of the regulation, as well as to collect stakeholder perspectives on the regulation and the implementation thereof.

The European Commission asked the contractor to address a series of 17 distinct evaluation questions that were linked to the above evaluation dimensions. These questions have formed the basis of the analysis and of the presentation of key findings hereafter.

Methodology

This study has drawn from a variety of data sources. Primary data was collected from targeted stakeholder groups using a series of interviews and online administered surveys. An online public consultation was performed to solicit input from individuals with a personal experience with rare diseases (patients and carers), and from health care professionals. Separately, the study team received unsolicited written contributions from stakeholders.

Several secondary data analyses were used to support the study. First, a comprehensive review of peer-reviewed and grey literature was conducted to contextualise findings and to address data gaps. A thorough analysis was also performed of the portfolio of data provided by the EMA on all designated and authorised orphan medicinal products.

Data on sales of orphan medicines in the European Union and on patent status of products was used to support a societal cost(-utility) analysis and estimate the economic value of the market exclusivity granted to designated orphan medicines in the EU.

Situation before 2000

The evaluation compared the landscape for orphan medicines at the end of 2017 to that before the EU Orphan Regulation went into effect in 2000. At that time, the landscape for medicines for the treatment of rare diseases in Europe was characterised by low levels of R&D activity and a large unmet medical need for treatments among patients with rare diseases. Depending on the definitions and data set used, it is estimated that there were between 15 and 70 products for rare diseases on the market in the EU. Access to such products was highly uneven.

In the absence of a clear commercial proposition, the pharmaceutical industry had shown little interest. The problem lay in large part with the small populations affected by each of these conditions, whereby pharmaceutical companies saw an uncertain business case around the technically demanding and costly development of innovative medicines. There had been some limited spill-over benefits in Europe from the earlier implementation of legislation to

support development of orphan medicines in the US and Japan. Europe's fragmented national regulatory systems and smaller populations meant the business case was never particularly strong. The lack of activity in the field of rare diseases was also observed in the research community.

The need for an EU regulation in this area was championed by various EU Member States as a legitimate and efficient response to a major social cost and health inequality where there was an evident market failure. Individual Member States had much less capacity and legal space to act effectively.

These observed issues ultimately contributed to the creation of the EU Orphan Regulation (EC) No 141/2000, which was officially adopted in 1999.

The EU Orphan Regulation No 141/2000 and regulatory framework

The EU Orphan Regulation shares not only its overarching objectives with the US Orphan Drug Act, but also substantial parts of its design. It offers developers a set of financial and other incentives to encourage investment in the development of orphan medicines.

To qualify for these incentives, a product should be intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition that either affects no more than five in 10 thousand persons in the EU, or would not otherwise be economically viable without incentives. It should also be demonstrated that there is no satisfactory alternative or that the product offers significant benefit over other available products. All applications are assessed by a hereto created body, the Committee for Orphan Medicinal Products.

If an orphan designated product meets all the requirements at the time of marketing authorisation, it is granted a period of 10 years of market exclusivity in the EU. During this time no other treatment for the same condition will be allowed onto the market, if it is considered similar. Other incentives offered are fee waivers and access to a special form of scientific advice known as protocol assistance. The EU Orphan Regulation also foresees in the ability for Member States and the EU to provide additional aid for research. The centralised procedure for marketing authorisation has been mandated to facilitate a single market.

Alongside the EU Orphan Regulation, a series of guidelines, notices and implementing regulations have been developed that together make up the regulatory framework.

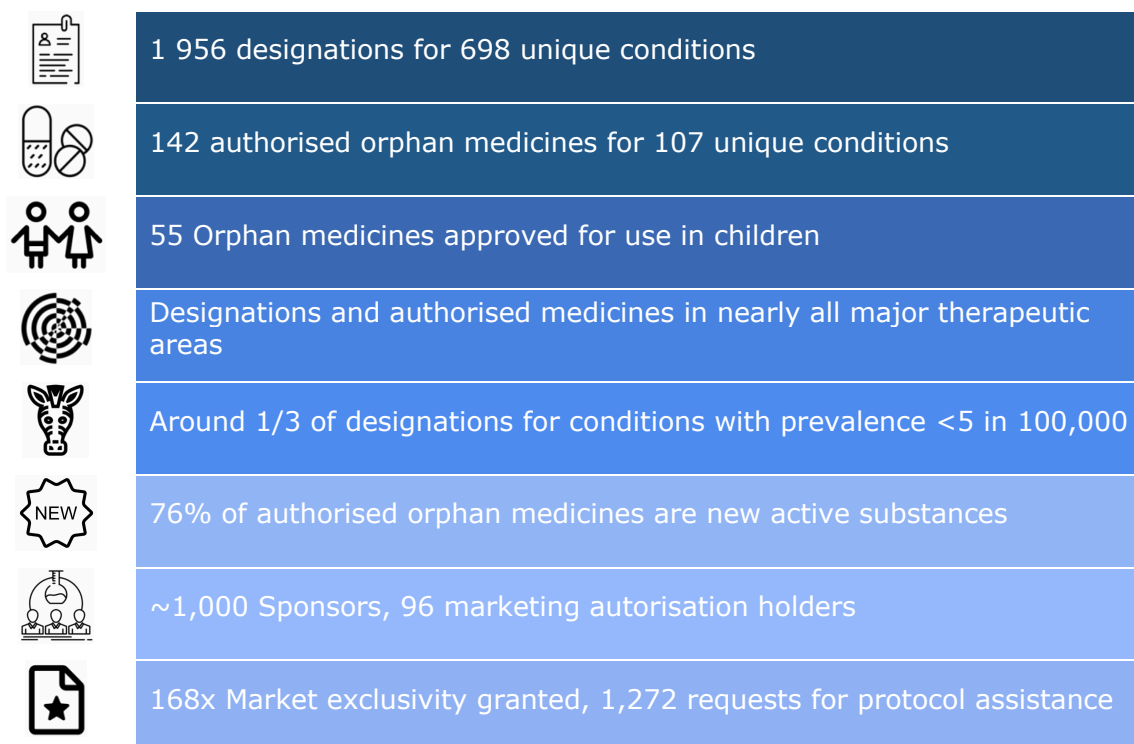
State of Play

The situation in Europe has changed in the 19 years since the introduction of the EU Orphan Regulation, with regard to the stock of available orphan medicines and the level of investment in R&D relevant to rare diseases.

Using data on the portfolio of designated and authorised orphan medicines provided by the EMA, and using sales data in the EU/EEA an extensive analysis

of the various outputs, outcomes and impacts of the EU Orphan Regulation was performed. Some key statistics have been summarised in Figure 1.

Figure 1 Overview of key outputs and results of the EU Orphan Regulation (2000-2017)



Since the Regulation went into effect, the level of activity to develop new treatments for rare diseases has markedly increased. By the end of 2017, 142 orphan medicines had been authorised. These cover a wide range of conditions and indications, including many very rare diseases. Based on estimates of disease prevalence and the population size in the EU, it is estimated that a maximum of 6.3 million people stand to benefit from these treatments. In reality, though, orphan medicines target sub-sets of such patients, based on factors such as disease stage and severity, age, or presence of certain gene mutations. Therefore, the actual treatment population of patients at any time is only a portion of this.

The rise in the number of new treatments available to patients since 2000 has been accompanied by improvements in the speed with which products enter the market, and the number of countries in the EU/EEA region where products are launched. The availability of treatments, however, remains highly uneven across the EU. Moreover, increasing price pressures are posing barriers to access.

As a result of the increase in (applications for) orphan designations, uptake of the incentives provided by the EU Orphan Regulation has also risen sharply. Market exclusivity was granted a total of 168 times, with 20 products receiving more than one period of market exclusivity (for 46 indications).

A growing proportion of Europe's pharmaceutical and biotechnology companies have become involved with rare disease research and the development of orphan medicines. The EMA has processed the applications of around 1,000 sponsors in the past 18 years. Over 70 have an EU authorised orphan medicine on the market.

The public sector's annual expenditure on rare disease research has increased across the period, from several tens of millions of Euros in the late 1990s to several hundred millions of Euros each year in 2018.

Relevance

To what extent have the specific objectives underlying the adoption of the Orphan Regulation proven to be appropriate for addressing the problems? To what extent is the current scope of application of the Regulation catering for real (unmet) needs of patients? To what extent has, the Orphan Regulation addressed the issue of return on investment?

Key data

- Approx. 50% of 105 analysed orphan medicines have an average annual sales revenue of €10 million or less in the EU; Approx. 15% show annual sales revenues of more than €100 million.
- For 2000-2017, across 105 orphan a total sales volume of €44.1 billion in the EU was calculated.
- Annual sales of active orphan medicines increased from €2.5 billion in 2008 to € 6.3 billion in 2016.
- 70% (74 out of 105 products analysed) of all authorised orphan medicines were still protected by a primary patent or SPC at the time of their authorisation.
- The average extension of the term of protection offered by the market exclusivity, beyond patent or SPC protection, is 3.4 years.
- 12 products have been authorised for more than one orphan indication. For 10, all indications were authorised at the same time.

The specific objectives of the Regulation were appropriate to the identified problem of observed market failure. The decision to move forward with an EU Regulation, rather than an EU Directive, meant legislation was applicable immediately across all Member States, thereby avoiding delays and inconsistency in implementation. This has helped to create a single (larger) market for orphan medicinal products.

Insufficient economic interest from the industry to develop medicines for rare diseases is likely to have been an important contributor to the lack of orphan medicines being developed, though it was by no means the sole reason. The provision of market exclusivity was therefore, in principle, an appropriate response to the evident market failure by offering developers an extension of the time during which they can recover their investment before competition emerges. However, its relevance varies substantially between products. For some products, the market exclusivity is effectively the only form of protection

against competition, but for others it may confer little to no additional protection against generic competition.

As it can reasonably be assumed that for a subset of products the market exclusivity has been a decisive factor in a sponsor's ability and willingness to develop the product and bring it to market, we conclude that the introduction of a market exclusivity incentive was a relevant and appropriate measure.

Even today, economic incentives appear to remain relevant to encourage development for certain products, as low turnovers can still be observed. At the same time, it should be recognised that today the orphan medicines market has changed and now includes numerous highly profitable medicines.

In this light, it is striking that sponsors have almost never sought to obtain orphan designation on the grounds of expectations of insufficient return to justify the necessary investment. This raises the question of whether orphan designations are currently not also granted to products where one could reasonably anticipate high returns on investment, simply because they address diseases that, within the context of the regulatory framework for the EU Orphan Regulation, are considered rare.

It is therefore timely and legitimate to consider whether, in certain areas and for some products, economic incentives that involve the use of public money are still required. To improve the overall effectiveness and efficiency of the Regulation, alternative or additional measures may prove more relevant.

To what extent are the provisions still an appropriate means for addressing one of the Regulation's main objectives, namely that patients suffering from rare diseases have access to the same quality of medicinal products as other patients within the EU? To what extent has this access been achieved across EU Member States and, if there are differences, what are the reasons for this?

Key data

- Before 2000, there were at least 70 products with a US orphan designation ('orphan-likes') available in at least one EU market.
- Products typically took 2 to 3 years to become available in the first EU12 Member State following marketing authorisation and after three years had reached 3 to 4 EU-12 Member States
- The number of orphan medicines on the market in at least one EU Member State increased from 48 in 2008 to 129 in 2016.
- Large variations in overall availability and time-to-launch persist across the EU.

Since the introduction of the EU Orphan Regulation, the number of treatments for patients with rare diseases on the market has improved, with more products available, available faster and reaching a slightly higher number of markets. As such, it can be said that the 'gap' between patients with rare diseases and patients with more common diseases has narrowed. Nonetheless, there remains a very large unmet medical need, as for the large majority of rare diseases there remain no treatments available. The improved access to orphan medicines has

not been achieved equally across all EU Member States. Very substantial variations in availability and time-to-launch continue to exist between Member States.

Differences in national marketing authorisation procedures do not appear to have been an important source of that variation, even before the centralised procedure for marketing authorisation became mandatory (in 2004). Rather, a substantial part of the observed unevenness stems from national policies and decision-making processes.

These observations show that the objective of the EU Orphan Regulation to address the issue of availability of, and access to orphan medicines has not yet been met and remains as relevant today as it was when it was introduced.

In fact, as more orphan medicines are being developed, there is a real risk of increasing inequities in access to treatment for patients with rare diseases. This is because many such products are very expensive and countries within the EU/EEA region vary greatly in their ability and willingness to pay. As a result, marketing authorisation holders are largely ignoring smaller and less attractive markets. Simultaneously, increasing price pressures may force more countries to adopt restrictive reimbursement policies. Within the EU Orphan Regulation there are neither the tools nor the mandate to intervene at this level.

Which developments in the sector (e.g. advanced therapies, personalised medicine, scientific developments, use of real-world data, sustainability of national health care systems) have significant implications for the Regulation's relevance and future?

Key data

- The share of advanced therapies has sharply increased to around 11-20% of all new designations in the period 2010-2017. By the end of 2017, 4 advanced therapies with an orphan designation had been authorised.
- Personalised medicine may hold great promise in, among other things, improving the effectiveness of treatments. It may also significantly increase the number of products brought to market with an orphan designation by enabling the creation of 'orphan subsets' of more common diseases.
- Of the 63 orphan medicines authorized in the EU between 2000-2010 only 38 completed a randomised clinical trial; of these one third involved fewer than 100 patients.

There have been a number of scientific developments that have dramatically altered, or have the potential to do so, the development of new treatments for rare diseases. Developments of great significance include advanced therapies, personalised medicine and new trial designs.

These developments mostly have had, or will have, a clear positive impact on the number of new treatments developed for patients with rare diseases. Yet, they also pose challenges to the framework and application of the EU Orphan Regulation. A specific area of tension relates to the use of biomarkers to define

a medical condition or a valid sub-set for orphan designation. There is a widely held fear that personalised medicine will stretch the boundaries of the current regulatory framework by redefining what constitutes a rare disease and that, ultimately, all conditions could be considered as rare. Here, the general sense is that the current framework is not adequate to accommodate the identified challenges.

Another challenge posed is that stemming from the use of novel trial designs. These are increasingly giving rise to questions on what evidence base regulatory agencies and health technology assessors consider acceptable for decision-making. Although such designs may represent the best opportunity for collecting information in a challenging field of research, it requires further engagement between developers on the one hand and regulators and downstream decision-makers on the other to clarify mutual expectations.

Effectiveness

How have the developers made use of the specific incentives provided by the Regulation and what were the reasons behind this?

Key data

- Market exclusivity was granted 168 times.
- Protocol assistance was requested 1,272 times.
- The reported value of fee reductions totalled €115 million.

The various incentives all contribute to the development of new treatments for rare diseases. The effectiveness of incentives varies, based on factors such as the experience of the developer, market and product characteristics, the stage of development of the product and various other factors.

Market exclusivity is valued for helping to improve the earnings potential of orphan medicines, thus lowering financial barriers to product development. The incentive has most value to parties at the end of the development process, who are most likely to bring a product to market. The potential for obtaining market exclusivity, represented by the orphan designation, also helps to attract investors.

Protocol assistance is valued most by product developers with limited prior experience in seeing a product through clinical development. Its effectiveness in improving chances of success, however, is inconclusive.

Fee reductions and waivers play the largest role for small and medium-sized enterprises (for whom fees are waived entirely) and other parties with limited financial resources. However, for the latter, the remaining fees can still pose an obstacle.

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.

To what extent is the Orphan Regulation effective in addressing unmet medical needs?

Key data

- Designations have been granted to products in 14 major areas of the Anatomical Therapeutic Chemical (ATC) Classification System; products have been authorised in 13 areas.
- The largest share of products (28% of designations; 34% of authorised products) consists of anti-cancer treatments; clustering around orphan indications also occurs most strongly for forms of cancer.
- Designations were granted for 698 unique orphan indications; products were authorised for 107 unique orphan indications.
- As of 2014, around 1 in 5 designations is for a new orphan indication.
- Demonstration of significant benefit was required for 72% of authorised products.
- For 61% of unique orphan indications there is only 1 designation.
- For 82% of unique orphan indications only 1 product has been authorised.
- Around a third of products are treatments with a prevalence of less than 5 in 100,000 (30% of designations, 35% of authorised products).

We assessed the impact of the Regulation to have been that:

- 21 additional orphan medicines have been developed and introduced in the EEA in 2000-2017.
- the average time-to-market has decreased by, on average, 9 months.
- Orphan medicines are available three years after market introduction, to, on average, 2.7% of total EU population (or 14 million citizens).

Since the introduction of the EU Orphan Regulation, a large number of products have been granted orphan designation and the number of authorised treatments has significantly increased. These new products make a useful contribution to addressing the hitherto unmet needs of patients with rare diseases, including many very rare conditions. However, in terms of bringing treatments to market in areas where none existed before, the Regulation shows a diminishing rate of return: today, only around a quarter of new orphan medicines brought to market are for conditions for which no alternative treatment options exist and fewer than one in five orphan designations are granted for conditions for which no other medicines had previously been granted this status.

Whilst authorised products cover a wide range of areas and indications, a certain clustering can be observed, particularly around oncological treatments. This has been associated with a number of factors, including availability of scientific leads, alignment with existing R&D portfolio's, and the availability of other treatment options. However, it is likely not coincidental that clustering is seen primarily in areas that are more likely to have a higher return on investment.

At the level of access to authorised treatments, some improvements have happened under the EU Orphan Regulation. Products are reaching more patients and are reaching them faster.

Overall, the EU Orphan Regulation has contributed to addressing some of the unmet needs for patients with rare conditions, but the unmet need remains considerable, in terms of availability of treatments as well as of access.

To what extent has the (additional) incentive for the development of 'orphan paediatric medicine' resulted in new medicinal products catering for an unmet medical need for children?

Key data

- 76% of all designations and 78% of authorised products are for conditions that affect (also) children.
- 55 (39%) authorised orphan medicines have been approved for use in children.
- 44 products have been authorised for forms of cancer that affect (also) children; 13 of these are approved for use in children.

A large number of products have been authorised for conditions affecting adults and children. However, less than half of these have been approved for use in children. This suggests the Regulation has not been sufficiently effective in helping to bring products to market for this particular group. Although the lack of development for paediatric use is seen across therapeutic areas and indications, it is most acutely felt in the area of paediatric oncology.

The primary reason cited by sponsors to (not) develop treatments for conditions primarily affecting children is the fit with the existing R&D portfolio. Insufficient development of products for paediatric indications, in case of conditions affecting both children and adults, on the other hand has also been linked to the fact it is not allowed to hold orphan and non-orphan indications under a single marketing authorisation.

Problems with paediatric development of orphan medicines relate, in part, to the interplay between the EU Orphan Regulation and EU Paediatric Regulation, as discussed further.

To what extent the Orphan Regulation and its implementation contributed to the general objective of competitiveness of European pharmaceutical industry? What were factors supported or hindered attaining this objective?

Key data

- There are approx. 1,000 unique entities listed as sponsor
- 87% of all designations and 100% of authorisations are held by pharmaceutical and biotechnology companies (including SMEs).
- SMEs account for approx. 40% of designations
- 53% of sponsors are headquartered in the EU/EEA
- Designations have been transferred between sponsors 640 times
- Transfer of sponsorship happens in equal measure to and from the EU/EEA

The EU Orphan Regulation has strengthened the climate for R&D for rare diseases, with a marked increase in the number of actors in the field, both in academia and in industry.

Pharmaceutical companies and SMEs hold the vast majority of all designations and all marketing authorisations. Nonetheless, smaller players such as academic institutions also play a part, mostly in the earlier stages of the development process. There is no clear indication that EU/EEA-based companies play a more significant role in some parts of the ecosystem than in others.

As there is no requirement for R&D to be performed in the EU/EEA, the Regulation does not have the means to directly influence industry competitiveness. In fact, decision-making on where R&D activities are conducted depends largely on other factors, such as the ability to conduct clinical trials, the presence of research networks and availability of researchers, as well as economic R&D incentives (e.g. tax breaks). The EU Orphan Regulation thus only can make an indirect contribution to the competitiveness of the European pharmaceutical industry, which could not be quantified.

Are the provisions of the Orphan Regulation sufficiently explicit as to when market exclusivity should be granted and revoked?

Key data

- No record is kept of grounds for voluntary withdrawal of orphan designation by sponsors.
- Reduction of the market exclusivity was requested once by a Member State; the EMA found, however, that the eligibility criteria remained fulfilled.

Granting of market exclusivity is dependent on the assessment whether the product still fulfils all the designation criteria at the time of marketing authorisation. Whereas the criteria are sufficiently explicit, sponsors sometimes struggle to meet these, particularly when demonstration of significant benefit is concerned.

Sponsors indicate that they sometimes opt to withdraw their designation due to associated costs of maintaining separate marketing authorisations for orphan and non-orphan conditions.

Although the Regulation contains a provision that would allow the market exclusivity to be reduced to 6 years in case the eligibility criteria are no longer fulfilled, in practice this has not happened. The lack of use of this provision, and consequently its effectiveness, relates to how it has been formulated: reassessment can only be done on the basis of the original grounds of designation. Consequently, the market exclusivity period for a product designated on the basis of prevalence cannot be reduced on the basis of its realised profit.

A second reason is that the reassessment can only be requested by Member States. These do not generally have the resources and information needed to monitor whether a request for reassessment is reasonable. They have therefore argued that the responsibility should be shifted to the EMA. It is clear that in its current form the Regulation is explicit, yet not very effective in providing the possibility to revoke market exclusivity after a product has been authorised.

Efficiency

Are the costs borne by the individual stakeholder reasonable in relation to the benefits (for the specific group)? Is there a fair distribution of costs between the main actors?

Key data

Our assessment of societal costs and benefits reveals a large uncertainty on the size and distribution of costs for stakeholders as a result of the Orphan Regulation in 2000-2017. The reference analysis gives the following results, but should be seen as indicative, as the data availability does not allow a high level of certainty:

- Developers have spent €11 billion more on R&D on orphan medicines as a result of the EU Orphan Regulation.
- Additional sales revenues as a result of EU authorised orphan medicines are largely in line with extra costs for R&D and production.
- The extra revenue attributed to the market exclusivity was €5 billion.
- Costs to health systems from treatment with orphan medicines have risen by approx. €20-25 billion.
- Fee waivers and protocol assistance are valued at €0.2 billion.
- National governments and the EU have contributed €0.8 billion to research for rare diseases.
- For 24 orphan medicines, the average incremental cost-effectiveness ratio is €110,000, with a weighted average of €54,000 per quality-adjusted life year.
- The accumulated health impact realised from authorised orphan medicines is estimated at 200,000 to 410,000 quality-adjusted life years (2000-2017).

For developers of orphan medicines, the extra costs and revenues as a result of the EU Orphan Regulation are, on average, fairly balanced, but the margin of uncertainty is high.

For health systems, the net effect of extra additional costs (from treatment with the new medicines) and cost-savings (from reduced illness or the fact that other treatments are no longer used) could not be established due to a lack of publicly available information.

Patients living with rare diseases are the main beneficiaries, resulting from reduced morbidity and mortality and an improved quality of life. There are likely to have been also wider economic benefits for patients, carers and others, such as impacts on (informal) care, productivity, quality of life of relatives. However, the size of these could not be established at the level of the EU Orphan Regulation, mainly due to the large variation in conditions targeted. It is likely to be a positive value, though, given the fact that rare diseases are often highly disabling and represent a heavy burden for all.

The societal costs that directly relate to the incentives of the EU Orphan Regulation (€5 billion for market exclusivity, €1 billion for other incentives) are much smaller than additional expenses due to the improved accessibility to products.

The societal costs per QALY for authorised orphan medicines frequently exceed the indicative reference values used by some national governments. However, while according to HTA reports many orphan medicines are expected to deliver health improvements at high costs per QALY, those that are actually on the market and reimbursed are generally more cost-effective.

Whether this distribution of costs and benefits is 'fair' is an entirely subjective matter, as it depends on what value one places not only on an individual human life but also on what implications this valuation has for society as a whole. Therefore, this study refrains from drawing any conclusions on the fairness of the distribution, leaving this to policy makers and the public at large with the here presented data in hand.

Could the objectives of the Orphan Regulation have been achieved differently, i.e. at lower costs?

Key data

- Approx. 10 to 12% of designations result in an authorised product.
- 12 products have been authorised for two or more orphan indications, 75% of which are oncological.
- 77% of authorised products are new active substances; 19% are well-established use products or known-active substances.

Although the administrative costs of applying the EU Orphan Regulation are comparatively small, they are not negligible to the stakeholders involved. A relatively small cost saving could be realised if the process of evaluation of applications could be optimised, for instance by requiring applicants to submit more complete and better quality data dossiers than is currently the case.

A much larger cost element relates to the health costs resulting from the treatment of patients with orphan medicines. The market exclusivity reward provides the opportunity for sponsors to have a longer period in which the product is protected from competition and higher prices can be realised. Undesirable effects or, from a societal cost perspective, inefficiencies can arise in situations where the proportionality between the market exclusivity reward and the costs of product development is in question.

Products that have been authorised for multiple orphan indications have a larger patient basis and can thus realise more turnover. Moreover, consecutive periods of market exclusivity prolong the protection period and potentially delay generic competition for longer than desirable. The ability to obtain multiple orphan indications and periods of market exclusivity on a single product, without differentiation, increases the risk of overcompensation.

The risk of lack of balance between reward and cost also exists for products that have not been developed as new active substances. The current regulatory framework for the EU Orphan Regulation does not contain any provision to safeguard the affordability and accessibility of products even when no significant R&D investments have been made by the sponsor. Applications such as those for well-established use products and known active substances receive the same reward as new active substances.

The market exclusivity period of 10 years does not appear to offer an unreasonable compensation for an orphan medicine compared to non-orphan medicines, taking into account both lower revenue potential and lower R&D costs. However, there is a risk of overcompensation if the annual turnover is substantially above € 100 million, or in case of low development costs. In case of multiple authorised orphan indications such a level may be reached more easily. In case of well-established use products and known active substances, overcompensation may occur because the R&D costs may be below average.

In the absence of good estimates of R&D costs at product level, it cannot be said how often overcompensation occurs. What is clear is that efficiency gains could be realised if the market reward would be related better to product prices, realised sales and R&D costs.

Another area that would help to improve the cost-benefit ratio of the EU Orphan Regulation relates to the outcome of the regulation, i.e. the health impact. We notice that for many orphan medicines cost-effectiveness data are not available. This means that decisions to allow orphan medicines to enter national markets may not always be based on cost-effectiveness observations. If more extensive economic information would be available, it could assist in better-informed decision making by authorities.

How significant is the administrative burden for specific stakeholders caused by the Orphan Regulation compared to the situation before it entered into force?

Key data

- The EU Orphan Regulation has no mandatory requirements for developers of orphan medicines. Application for orphan designation is voluntary.
- The COMP has 28 members representing the Member States, 3 expert members nominated by the EC, and 3 patient representatives.
- COMP members and their home institutions are not compensated for their work.
- The COMP currently meets 1x per month, for 3 days.

The EU Orphan Regulation is a voluntary instrument that does not impose any requirements on developers of orphan medicine that choose not to make use of the Regulation. As such, there is no real administrative burden on this group of stakeholders who appear to be generally satisfied with the regulatory framework and its application.

There is some administrative burden resulting from the Regulation at the level of the EMA. These costs are relatively small but are likely set to increase as the number of applications continues to grow. The issue of increasing workload likewise affects the members of the COMP. The administrative burden associated with the work performed by COMP members largely falls on their home institutions who are not compensated. This is putting serious strain on the system and could affect its long-term sustainability.

Coherence

To what extent is the Orphan Regulation coherent/complementary with other EU and national interventions in the pharmaceutical area?

The EU Orphan Regulation has clear links with the Paediatric Regulation (1901/2006/EC), the Regulation for Advanced Therapy Medicinal Products (No 1394/2007/EC) and the Regulation concerning supplementary protection certificates for medicinal products (469/2009/EC). It also fits within the overarching EU pharmaceutical policy framework. This complementarity is recognised by stakeholders.

This, however, does not mean that the different regulations and policies all work together to optimal effect. This is most apparent in the interplay between the EU Orphan Regulation and the Paediatric Regulation. There is a lack of development of treatments for children with rare diseases. Apparently, the two Regulations that should cater for this population (namely, the Orphan and Paediatric Regulation) do not offer the necessary incentives to steer development towards this important area. More generally, it has been noted that the overall regulatory system for pharmaceutical products is rather complex and would benefit from a more holistic and streamlined architecture. The complexity is seen, for instance, in the use of apparently similar yet distinct

concepts (e.g. significant benefit and added value) between regulations and in how different assessment processes are organised with respect to each other.

Stakeholders from, in particular, national public authorities also expressed some concerns about the fact that, for some orphan medicines, sponsors have the ability to 'switch' between the protections offered by the EU Orphan Regulation and the Paediatric Regulation (i.e. orphan market exclusivity and paediatric SPC extension, respectively). This creates uncertainty for generics manufacturers about the exact term of the protection, which can further delay the entry of competition into the market.

The EU Orphan Regulation has played an important role in encouraging the implementation of various complementary, non-legislative EU initiatives. The EU Orphan Regulation creates the policy framework to support development of orphan medicines, whilst other EU actions support the infrastructure within which R&D takes place.

There are good links between the EMA on the one hand, and the national health authorities and health technology assessment agencies on the other. These parties are aligned in their objectives to provide patients with rare diseases the necessary treatments, recognising the role played therein by the pharmaceutical industry. However, stakeholders from different interest groups (e.g. sponsors, national public authorities, patient organisations) have expressed concerns about the apparent lack of coherence between national policies for decision making on pricing and reimbursement of orphan medicines, which is contributing to variations in access throughout the EU/EEA. The current Commission proposal for an EU Regulation on Health Technology Assessment, if adopted, may be a necessary next step to achieve a higher level of convergence in health technology assessment methodologies and greater coherence between the EU procedures for marketing authorisation and national procedures for medicines reimbursement.

To what extent do the various tools (incentives, procedures, assistance) as set out in the Orphan Regulation work together in a coherent way?

The EU Orphan Regulation is internally coherent: it offers a set of incentives that work well together and are of relevance to both smaller and larger developers. Each of the tools or incentives that is part of the EU Orphan Regulation has its own objectives and value and addresses distinct needs across the product development lifecycle.

The various EMA committees cooperate reasonably well, though room for improvement exists in, for example, the alignment of internal processes within the EMA.

What are the links between the areas of orphan and paediatric medicines? To what extent, in practice, is there an overlap and how has this influenced therapeutic advances?

As around 50% of all rare diseases manifest in childhood, there is a clear need for the development of orphan medicines for paediatric indications. It is therefore appropriate that there is an explicit link between the EU Orphan Regulation and the Paediatric Regulation, in the form of an extension of the

period of market exclusivity for orphan medicines for which paediatric investigations were completed. Nonetheless, our analysis shows that only half of all currently authorised orphan medicines have been approved for use in children.

As mentioned before, this lack of development of treatments for children with rare diseases may relate, at least in part, to the fact that – even together – the Orphan Regulation and Paediatric Regulation do not provide the necessary stimuli to direct developers towards this important area. The sub-optimal interaction between the Regulations can be seen, for instance, in how conditions are defined. Normally, the EU Orphan Regulation framework will aim to define conditions as broad as possible to include all potential therapeutic indications. The tendency is then to consider both adult and paediatric populations together. However, this approach could mean the product is not eligible for orphan designation even though the sub-set represented by the paediatric population alone would be. Only if the paediatric sub-set is approved as an orphan indication can the EU Orphan Regulation provide the necessary incentives (including extension of the market exclusivity upon completion of the paediatric investigations). If this does not occur, the Paediatric Regulation still mandates the conduct of paediatric investigations and will reward the completion thereof. However, it does not specifically incentivise or reward successful development for paediatric application.

In the consideration of waivers from paediatric investigations, issues were also identified that impede the development of medicines for paediatric patients. This applies particularly in the field of oncology.

To which extent is the concept of designation consistent with the marketing authorisation itself?

There is a measure of inconsistency between the concepts of orphan designation and the marketing authorisation for orphan medicines. For one, only a small share of designations is eventually converted into authorised products. This may unduly raise the expectations of patients with conditions for which products have been designated, but where none are successfully developed. This is, however, no different than in other areas of product development.

Some measure of inconsistency exists also between the application of the concepts of orphan indication, which is used for designations, and therapeutic indication, which describes for whom an authorised treatment can be used. Here too, though, it is not clear that this poses a real problem or if it would be easily avoidable.

EU added value

What has been the added value resulting from EU intervention in the Orphan Regulation compared to what could be achieved at international, national or regional level without such intervention?

The value offered by the EU Orphan Regulation above and beyond similar Regulations in other jurisdictions, in particular the US, as well as beyond national level efforts is difficult to establish. The reason for this is that this requires projecting a situation that has not taken place. Nevertheless, an

attempt was made to estimate this added value against a comparator situation without the Regulation and by relating this to the baseline situation before 2000.

This study finds that the EU Orphan Regulation has contributed to an increase in the number of orphan medicines that have been developed and that are brought to market in the EU. Whilst the analysis itself is based on a number of assumptions and there is substantial uncertainty in the estimate provided, the EU Orphan Regulation is thought to have led to around 21 additional orphan medicines. As mentioned previously, this impact has occurred alongside somewhat faster access to EU markets and a slight increase in the number of EU markets where products are available. It is also found that the number of EU markets in which orphan medicines are available increases over time. Whilst all these effects are, on average, positive, there is no equity among Member States in how these benefits have been distributed.

As the results are based on statistical analysis and no individual products can be identified that could be linked entirely to the EU Orphan Regulation, it is not possible to conclude which groups of patients have benefitted most directly from the EU Orphan Regulation. Comparison against the baseline situation shows no major trend breaks in the allocation over therapeutic areas, though this conclusion is complicated by the very low numbers of products in some areas.

Overall, it is reasonable to state that the EU Orphan Regulation has allowed for a more concerted and effective response to the challenge of market failure in the development of orphan medicines than would have been possible at the level of the individual Member States alone. It has also acted as a catalyst to the efforts made by the Member States in the field of rare diseases and orphan medicines. The market exclusivity offered to EU authorised orphan medicines has been identified as one of the key incentives offered by the Regulation. This would not have been possible at the level of an individual Member State, as it would have led to distortions of the internal market.

What is the value of non-legislative initiatives in the field of rare diseases (registries, information/epidemiological databases, etc.) for the proper functioning of the Orphan Regulation?

Substantial added value has been brought by the efforts of the EU in terms of cooperation and research funding for rare diseases and orphan medicines. The Commission contributes to a wide variety of non-legislative initiatives. These initiatives offer added value by bringing together stakeholders and bundling expertise and data. As such, they complement the EU Orphan Regulation by strengthening the field of rare diseases research and orphan medicine development

Concluding remarks

This study finds that the EU Orphan Regulation has contributed to important strides in the field of rare diseases and development of orphan medicines. Since the Regulation was introduced more products have come on the market. There is also a promising pipeline of products under development, that may bring real value to patients for whom currently no treatment options exist.

The needs and problems to which the EU Orphan Regulation responded still exist and, as such, the objectives of the Regulation remain as important today as they were nearly two decades ago.

Notwithstanding these important successes, this study has shown that progress has not been even in all areas. The EU Orphan Regulation has also produced some unintended effects that in 2000 were either not foreseen, or for which the magnitude of their impact could not be predicted. It is therefore timely to consider various aspects of the regulatory framework for orphan medicines in the EU.

The present study was not tasked with drawing up recommendations or preparing policy options for the future of the EU Orphan Regulation. Instead, its focus was retrospective, whilst identifying areas of tension that could impact the Regulation in future. Where stakeholders offered up specific recommendations or points for consideration, these have been included in the report.

Sommaire exécutif

Objectifs de l'étude

Cette étude soutient une évaluation conjointe complète du règlement de l'UE concernant les médicaments orphelins et du règlement de l'UE sur les médicaments à usage pédiatrique. La présente étude a permis de recueillir de l'information sur cinq dimensions de l'évaluation : A) pertinence, B) efficacité, C) efficience, D) cohérence et E) valeur ajoutée européenne du règlement européen sur les orphelins. L'objectif était de réunir et d'analyser des informations factuelles sur les résultats et les impacts du règlement, ainsi que de saisir les points de vue des parties prenantes sur le règlement et sa mise en œuvre.

La Commission européenne a demandé au contractant de répondre à une série de 17 questions d'évaluation distinctes qui étaient liées aux dimensions d'évaluation ci-dessus. Ces questions ont servi de base à l'analyse et à la présentation des principales conclusions ci-après.

Méthodologie

La présente étude a été réalisée à partir de diverses sources de données. Les données primaires ont été recueillies auprès de groupes intéressés ciblés au moyen d'une série d'entrevues et de sondages en ligne. Une consultation publique en ligne a été menée afin de recueillir les commentaires de personnes ayant une expérience personnelle des maladies rares (patients et soignants) et de professionnels de la santé. Par ailleurs, l'équipe chargée de l'étude a reçu des contributions écrites non sollicitées de la part des parties prenantes.

Plusieurs analyses de données secondaires ont été utilisées à l'appui de l'étude. Tout d'abord, un examen exhaustif de la documentation évaluée par les pairs et de la littérature grise a été effectué afin de contextualiser les résultats et de combler les lacunes dans les données. Une analyse approfondie du portefeuille de données fournies par l'EMA sur tous les médicaments orphelins désignés et autorisés a également été réalisée.

Les données sur les ventes de médicaments orphelins dans l'Union européenne et sur le statut de brevet des produits ont été utilisées pour étayer une analyse coût (-utilité) sociétale et pour estimer la valeur économique de l'exclusivité commerciale accordée aux médicaments orphelins désignés dans l'UE.

Situation avant 2000

L'évaluation a comparé la situation des médicaments orphelins à la fin de 2017 à celui d'avant l'entrée en vigueur du règlement européen sur les médicaments orphelins en 2000.

A l'époque, le paysage des médicaments destinés au traitement des maladies rares en Europe se caractérisait par un faible niveau d'activité de R&D et un besoin médical important non satisfait en matière de traitements parmi les patients atteints de maladies rares. Selon les définitions et l'ensemble de données utilisé, on estime qu'il y avait entre 15 et 70 produits pour les maladies rares sur le marché de l'UE. L'accès à ces produits était très inégal.

En l'absence d'une proposition commerciale claire, l'industrie pharmaceutique a montré peu d'intérêt. Le problème résidait en grande partie dans les petites populations touchées par chacune de ces conditions, où les sociétés pharmaceutiques ont vu une analyse de rentabilisation incertaine autour du développement techniquement exigeant et coûteux de médicaments innovants. Il y a eu quelques retombées positives limitées en Europe en raison de la mise en œuvre antérieure de la législation visant à soutenir le développement des médicaments orphelins aux États-Unis et au Japon. En raison de la fragmentation des systèmes réglementaires nationaux en Europe et des populations moins importantes, l'analyse de rentabilisation n'a jamais été particulièrement solide. Le manque d'activité dans le domaine des maladies rares a également été observé dans la communauté des chercheurs.

La nécessité d'une réglementation européenne dans ce domaine a été défendue par plusieurs États membres de l'UE comme une réponse légitime et efficace à un coût social majeur et à une inégalité en matière de santé lorsqu'il y avait une défaillance manifeste du marché. Les États membres individuels avaient beaucoup moins de capacité et d'espace juridique pour agir efficacement.

Ces problèmes observés ont finalement contribué à l'élaboration du règlement (CE) n° 141/2000, qui a été officiellement adopté en 1999.

Le règlement de l'UE n° 141/2000 concernant les médicaments orphelins et le cadre réglementaire

Le règlement de l'UE sur les médicaments orphelins partage non seulement des objectifs généraux avec l'«Orphan Drug Act» américaine, mais aussi des parties substantielles de sa conception. Il offre aux développeurs un ensemble d'incitations financières et autres pour encourager l'investissement dans le développement de médicaments orphelins.

Pour pouvoir bénéficier de ces incitations, un produit doit être destiné au diagnostic, à la prévention ou au traitement d'une maladie potentiellement mortelle ou chroniquement débilitante qui ne touche pas plus de cinq personnes sur 10 000 dans l'UE, ou qui ne serait pas économiquement viable sans incitations. Il doit également être démontré qu'il n'existe pas d'alternative satisfaisante ou que le produit offre des avantages significatifs par rapport aux autres produits disponibles. Toutes les demandes sont évaluées par un organisme créé par la présente décision, le comité des médicaments orphelins.

Si un produit désigné orphelin remplit toutes les conditions requises au moment de l'autorisation de mise sur le marché, il bénéficie d'une période d'exclusivité commerciale de 10 ans dans l'UE. Pendant ce temps, aucun autre traitement pour la même affection ne sera autorisé sur le marché s'il est considéré comme similaire. D'autres mesures incitatives sont l'exonération des frais et l'accès à une forme spéciale d'avis scientifiques connue sous le nom d'aide au protocole. Le règlement de l'UE sur les orphelins prévoit également la possibilité pour les États membres et l'UE de fournir une aide supplémentaire pour la recherche. La procédure centralisée d'autorisation de mise sur le marché a été mandatée afin de faciliter un marché unique.

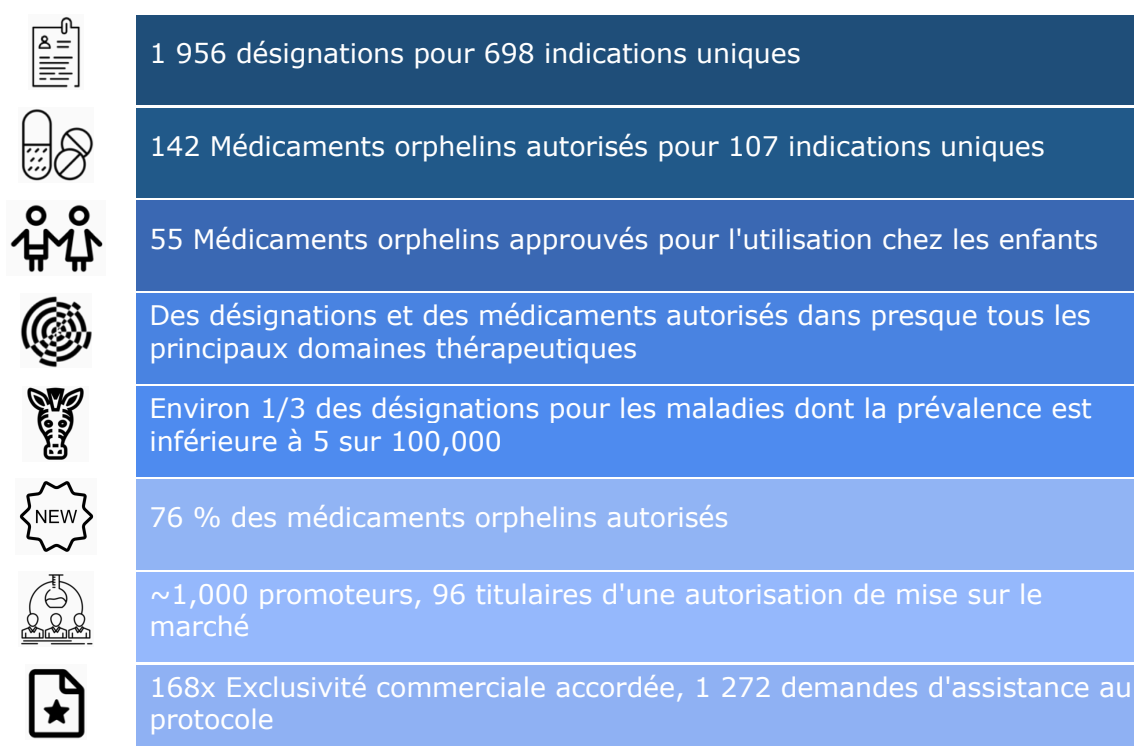
Parallèlement au règlement de l'UE sur les maladies rares, une série de lignes directrices, d'avis et de règlements d'application ont été élaborés, qui constituent ensemble le cadre réglementaire.

État d'avancement

La situation en Europe a changé au cours des 19 années depuis l'introduction du règlement de l'UE sur les médicaments orphelins, en ce qui concerne le stock de médicaments orphelins disponibles et le niveau des investissements dans la R&D pour les maladies rares.

En utilisant les données sur le portefeuille de médicaments orphelins désignés et autorisés fournies par l'EMA et les données sur les ventes dans l'UE/EEE, une analyse approfondie des différents produits, résultats et impacts du règlement européen sur les médicaments orphelins a été réalisée. Certaines statistiques clés ont été résumées à la figure 1.

Figure 1 Vue d'ensemble des principaux produits et résultats du règlement de l'UE sur les orphelins (2000-2017)



Depuis l'entrée en vigueur du règlement, le niveau d'activité pour développer de nouveaux traitements pour les maladies rares a considérablement augmenté. Fin 2017, 142 médicaments orphelins avaient été autorisés. Celles-ci couvrent un large éventail de maladies et d'indications, y compris de nombreuses maladies très rares. Sur la base des estimations de la prévalence de la maladie et de la taille de la population dans l'UE, on estime que 6,3 millions de personnes au maximum pourraient bénéficier de ces traitements. En réalité, les médicaments orphelins ciblent des sous-ensembles de ces patients, en fonction de facteurs tels que le stade et la gravité de la maladie, l'âge ou la présence de

certaines mutations génétiques. Par conséquent, le nombre réel de patients traités à un moment donné n'est qu'une partie de ce nombre.

L'augmentation du nombre de nouveaux traitements disponibles pour les patients depuis 2000 s'est accompagnée d'une amélioration de la rapidité avec laquelle les produits entrent sur le marché et du nombre de pays de l'UE/EEE où ils sont lancés. La disponibilité des traitements reste toutefois très inégale dans l'UE. En outre, les pressions croissantes sur les prix constituent des obstacles à l'accès.

En raison de l'augmentation du nombre de demandes de désignation d'orphelins, le recours aux incitations prévues par le règlement de l'UE sur les orphelins a également fortement augmenté. L'exclusivité commerciale a été accordée 168 fois au total, 20 produits ayant bénéficié de plus d'une période d'exclusivité commerciale (pour 46 indications).

Une proportion croissante des entreprises pharmaceutiques et biotechnologiques européennes se sont engagées dans la recherche sur les maladies rares et le développement de médicaments orphelins. L'EMA a traité les demandes d'environ 1 000 répondants au cours des 18 dernières années. Plus de 70 d'entre eux ont un médicament orphelin autorisé par l'UE sur le marché.

Les dépenses annuelles du secteur public pour la recherche sur les maladies rares ont augmenté au cours de la période, passant de plusieurs dizaines de millions d'euros à la fin des années 1990 à plusieurs centaines de millions d'euros par an en 2018.

Pertinence du règlement

Dans quelle mesure les objectifs spécifiques qui sous-tendent l'adoption du règlement relatif aux médicaments orphelins se sont-ils révélés appropriés pour résoudre les problèmes? Dans quelle mesure la portée d'application actuel du règlement répond-elle aux besoins réels (non satisfaits) des patients? Dans quelle mesure le règlement sur les orphelins a-t-il abordé la question du retour sur investissement?

Chiffres clés

- Environ 50% des 105 médicaments orphelins analysés ont un chiffre d'affaires annuel moyen inférieur ou égal à 10 millions d'euros dans l'UE ; environ 15% ont un chiffre d'affaires annuel supérieur à 100 millions d'euros.
- Pour la période 2000-2017, sur 105 orphelins, le volume total des ventes dans l'UE a été estimé à 44,1 milliards d'euros.
- Le chiffre d'affaires annuel des médicaments orphelins actifs est passé de 2,5 milliards € en 2008 à 6,3 milliards € en 2016.
- 70 % (74 des 105 produits analysés) de tous les médicaments orphelins autorisés étaient encore protégés par un brevet principal ou un CCP au moment de leur autorisation.

- L'extension moyenne de la durée de protection offerte par l'exclusivité commerciale, au-delà de la protection par brevet ou CCP, est de 3,4 ans.
- 12 produits ont été autorisés pour plus d'une indication orpheline. Pour 10 produits, toutes les indications ont été autorisées en même temps.

Les objectifs spécifiques du règlement étaient adaptés au problème identifié de la défaillance du marché constatée. La décision d'aller de l'avant avec un règlement de l'UE, plutôt qu'avec une directive de l'UE, signifiait que la législation était immédiatement applicable dans tous les États membres, évitant ainsi des retards et des incohérences dans la mise en œuvre. Cela a contribué à créer un marché unique (plus vaste) pour les médicaments orphelins.

L'intérêt économique insuffisant de l'industrie pour le développement des médicaments contre les maladies rares a probablement contribué de manière importante à l'absence de médicaments orphelins, même si ce n'était en aucun cas la seule raison. L'octroi de l'exclusivité commerciale constituait donc, en principe, une réponse appropriée à la défaillance évidente du marché en offrant aux promoteurs une prolongation du délai pendant lequel ils peuvent récupérer leur investissement avant l'apparition de la concurrence. Toutefois, sa pertinence varie considérablement d'un produit à l'autre. Pour certains produits, l'exclusivité commerciale est effectivement la seule forme de protection contre la concurrence. Pour d'autres, elle peut néanmoins conférer peu ou pas de protection supplémentaire contre la concurrence générique.

Car on peut raisonnablement supposer que, pour un sous-ensemble de produits, l'exclusivité commerciale a été en effet un facteur décisif dans la capacité et la volonté d'un promoteur de développer le produit et de le mettre sur le marché, nous concluons que l'introduction de l'exclusivité commerciale comme incitation économique est une mesure pertinente et appropriée.

Aujourd'hui encore, les incitations économiques semblent toujours pertinentes pour encourager le développement de certains produits, puisque l'on observe encore de faibles chiffres d'affaires. En même temps, il faut reconnaître qu'aujourd'hui, le marché des médicaments orphelins a changé et comprend désormais de nombreux médicaments très rentables.

Dans ce contexte, il est frappant de constater que les promoteurs n'ont presque jamais cherché à obtenir la désignation orpheline parce qu'ils s'attendaient à un rendement insuffisant pour justifier l'investissement nécessaire. Cela soulève la question de savoir si les désignations orphelines ne sont actuellement pas également accordées à des produits pour lesquels on peut raisonnablement s'attendre à un retour sur investissement élevé, simplement parce qu'ils concernent des maladies qui, dans le contexte du cadre réglementaire du règlement européen sur les orphelins, sont considérées comme rares.

Il est donc opportun et légitime d'examiner si, dans certains domaines et pour certains produits, des incitations économiques impliquant l'utilisation de fonds publics sont encore nécessaires. Pour améliorer l'efficacité et l'efficience

globales du règlement, des mesures alternatives ou supplémentaires peuvent s'avérer plus pertinentes.

Dans quelle mesure ces dispositions constituent-elles encore un moyen approprié pour atteindre l'un des principaux objectifs du règlement, à savoir que les patients souffrant de maladies rares aient accès à des médicaments de la même qualité que les autres patients de l'UE? Dans quelle mesure cet accès a-t-il été réalisé dans les États membres de l'UE et, s'il existe des différences, quelles en sont les raisons?

Chiffres clés

- Avant 2000, il y avait au moins 70 produits ayant une désignation orpheline aux États-Unis (" orphan-likes ") disponibles sur au moins un marché de l'UE.
- Il fallait généralement 2 à 3 ans pour que les produits soient disponibles dans le premier État membre de l'UE-12 après l'autorisation de mise sur le marché et, après trois ans, dans 3 à 4 États membres de l'UE-12.
- Le nombre de médicaments orphelins sur le marché dans au moins un État membre de l'UE est passé de 48 en 2008 à 129 en 2016.
- D'importantes variations dans la disponibilité globale et le délai de lancement persistent dans l'UE.

Depuis l'introduction du règlement européen sur les médicaments orphelins, le nombre de traitements pour les patients atteints de maladies rares sur le marché s'est amélioré, avec plus de produits disponibles, disponibles plus rapidement et atteignant un nombre légèrement supérieur de marchés. En tant que tel, on peut dire que l'écart entre les patients atteints de maladies rares et les patients atteints de maladies plus courantes s'est réduit. Néanmoins, les besoins médicaux non satisfaits restent très importants, car pour la grande majorité des maladies rares, aucun traitement n'est encore disponible. L'amélioration de l'accès aux médicaments orphelins n'a pas été réalisée de la même manière dans tous les États membres de l'UE. Il existe toujours des variations très importantes entre les États membres en ce qui concerne la disponibilité et le délai de lancement des produits.

Les différences entre les procédures nationales d'autorisation de mise sur le marché ne semblent pas avoir été une source importante de cette variation, même avant que la procédure centralisée d'autorisation de mise sur le marché ne devienne obligatoire (en 2004). Au contraire, une part importante des inégalités observées provient des politiques nationales et des processus de prise de décision.

Ces observations montrent que l'objectif du règlement de l'UE sur les médicaments orphelins, qui est de répondre à la question de la disponibilité et de l'accès aux médicaments orphelins, n'a pas encore été atteint et reste aussi pertinent aujourd'hui qu'il l'était lorsqu'il a été introduit.

En fait, à mesure que de plus en plus de médicaments orphelins sont développés, il existe un risque réel d'accroître les inégalités à ce qui concerne l'accès aux traitements pour les patients atteints de maladies rares. Cela s'explique par le fait que beaucoup de ces produits sont très chers et que la capacité et la volonté de payer varient considérablement d'un pays de l'UE/EEE à l'autre. En conséquence, les titulaires d'autorisations de mise sur le marché ignorent en grande partie les marchés plus petits et moins attrayants. Simultanément, des pressions croissantes sur les prix pourraient obliger un plus grand nombre de pays à adopter des politiques de remboursement restrictives. Dans le règlement de l'UE sur les orphelins, il n'existe ni les outils ni le mandat pour intervenir à ce niveau.

Quels développements dans le secteur (par exemple, les thérapies innovantes, la médecine personnalisée, les développements scientifiques, l'utilisation de données réelles, la durabilité des systèmes nationaux de soins de santé) ont des implications significatives pour la pertinence du règlement et son avenir?

Chiffres clés

- La part des thérapies innovantes a fortement augmenté pour atteindre environ 11 à 20 % de toutes les nouvelles désignations au cours de la période 2010-2017. Fin 2017, 4 thérapies innovantes avec une désignation orpheline avaient été autorisées.
- La médecine personnalisée peut être très prometteuse, notamment pour améliorer l'efficacité des traitements. Elle peut également augmenter considérablement le nombre de produits mis sur le marché avec une désignation orpheline en permettant la création de " sous-ensembles orphelins " de maladies plus courantes.
- Sur les 63 médicaments orphelins autorisés dans l'UE entre 2000 et 2010, seuls 38 ont fait l'objet d'un essai clinique randomisé, dont un tiers a concerné moins de 100 patients.

Un certain nombre de progrès scientifiques ont radicalement modifié, ou ont le potentiel de le faire, le développement de nouveaux traitements pour les maladies rares. Parmi les développements d'une grande importance figurent les thérapies innovantes, la médecine personnalisée et les nouveaux plans d'essai.

Ces développements ont pour la plupart eu, ou auront, un impact positif évident sur le nombre de nouveaux traitements développés pour les patients atteints de maladies rares. Cependant, ils posent également des défis au cadre et à l'application du règlement de l'UE sur les orphelins. L'utilisation de biomarqueurs pour définir un état pathologique ou un sous-ensemble valide pour la désignation orpheline constitue une source de tension particulière. On craint généralement que la médecine personnalisée repousse les limites du cadre réglementaire actuel en redéfinissant ce qui constitue une maladie rare et qu'en fin de compte, toutes les maladies puissent être considérées comme rares. Ici, le sentiment général est que le cadre actuel n'est pas adéquat pour relever les défis identifiés.

Un autre défi posé est celui qui découle de l'utilisation de nouveaux plans d'essai. Ceux-ci soulèvent de plus en plus de questions sur la base de connaissances que les organismes de réglementation et les évaluateurs de technologies de la santé considèrent comme acceptable pour la prise de décision. Bien que de tels plans d'essai puissent représenter la meilleure possibilité pour collecter des informations dans un domaine de recherche difficile, elles exigent un engagement plus poussé entre les développeurs, d'une part, et les régulateurs et les décideurs en aval, d'autre part, afin de clarifier les attentes mutuelles.

Efficacité

Comment les développeurs ont-ils utilisé les incitations spécifiques prévues par le règlement et pour quelles raisons?

Chiffres clés

- L'exclusivité commerciale a été accordée 168 fois.
- L'aide au protocole a été demandée 1 272 fois.
- La valeur déclarée des réductions de frais s'élève à 115 millions d'euros.

Les différentes mesures incitatives contribuent toutes au développement de nouveaux traitements pour les maladies rares. L'efficacité des incitations varie en fonction de facteurs tels que l'expérience du promoteur, les caractéristiques du marché et du produit, le stade de développement du produit et divers autres facteurs.

L'exclusivité commerciale est appréciée parce qu'elle contribue à améliorer le potentiel de revenus des médicaments orphelins, réduisant ainsi les obstacles financiers au développement de produits. Cette incitatif a le plus de valeur pour les parties qui se trouvent à la fin du processus de développement, et qui sont les plus susceptibles de mettre un produit sur le marché. La possibilité d'obtenir l'exclusivité commerciale, représentée par la désignation orpheline, contribue également à attirer les investisseurs.

L'aide au protocole est surtout appréciée par les développeurs de produits ayant peu d'expérience préalable dans le développement clinique d'un produit. Son efficacité à améliorer les chances de succès n'est toutefois pas prouvée.

Les réductions et les dispenses de frais jouent le rôle le plus important pour les petites et moyennes entreprises (pour lesquelles les frais sont entièrement dispensés) et les autres parties dont les ressources financières sont limitées. Toutefois, pour ces derniers, les frais restants peuvent encore constituer un obstacle.

Les effets des incitations individuelles ne peuvent être isolés les uns des autres, et l'efficacité des incitations offertes par le règlement de l'UE sur les orphelins ne peut être considérée comme distincte de celle des incitations offertes par des réglementations similaires dans d'autres juridictions comme les États-Unis.

Dans quelle mesure le règlement sur les orphelins est-il efficace pour répondre aux besoins médicaux non satisfaits?

Chiffres clés

- Des désignations ont été accordées à des produits dans 14 domaines principaux du système de classification anatomique, thérapeutique et chimique (ATC) ; des produits ont été autorisés dans 13 domaines.
- La plus grande part des produits (28% des désignations ; 34% des produits autorisés) est constituée de traitements anticancéreux ; le regroupement autour des indications orphelines est également le plus fort pour les formes de cancer.
- Des désignations ont été accordées pour 698 indications orphelines uniques ; des produits ont été autorisés pour 107 indications orphelines uniques.
- A partir de 2014, environ 1 désignation sur 5 concerne une nouvelle indication orpheline.
- La démonstration d'un avantage significatif était requise pour 72 % des produits autorisés.
- Pour 61 % des indications orphelines uniques, il n'existe qu'une seule désignation.
- Pour 82 % des indications orphelines uniques, un seul produit a été autorisé.
- Environ un tiers des produits sont des traitements dont la prévalence est inférieure à 5 sur 100 000 (30% des dénominations, 35% des produits autorisés).

Nous avons évalué l'impact du règlement en ce sens :

- 21 médicaments orphelins supplémentaires ont été développés et introduits dans l'EEE en 2000-2017.
- le délai moyen de mise sur le marché a diminué de 9 mois en moyenne.
- Les médicaments orphelins sont disponibles trois ans après leur mise sur le marché, soit en moyenne 2,7 % de la population totale de l'UE (soit 14 millions de citoyens).

Depuis l'introduction du règlement de l'UE sur les médicaments orphelins, un grand nombre de produits ont obtenu la désignation orpheline et le nombre de traitements autorisés a considérablement augmenté. Ces nouveaux produits contribuent utilement à répondre aux besoins jusqu'ici non satisfaits des patients atteints de maladies rares, y compris de nombreuses maladies très rares. Cependant, en ce qui concerne la mise sur le marché de traitements dans des domaines qui n'existaient pas auparavant, le règlement fait apparaître un

taux de rentabilité décroissant : aujourd'hui, seulement environ un quart des nouveaux médicaments orphelins mis sur le marché traitent des conditions pour lesquelles il n'existe aucune autre option de traitement et moins d'une désignation orpheline sur cinq a été accordée à des conditions pour lesquelles aucun autre médicament ne bénéficiait auparavant de ce statut.

Si les produits autorisés couvrent un large éventail de domaines et d'indications, un certain regroupement peut être observé, notamment autour des traitements oncologiques. Cela a été associé à un certain nombre de facteurs, y compris la disponibilité de pistes scientifiques, l'harmonisation avec le portefeuille de R-D existant et la disponibilité d'autres options de traitement. Cependant, ce n'est probablement pas une coïncidence si la formation de grappes peut être observée principalement dans des secteurs qui sont plus susceptibles d'avoir un rendement du capital investi plus élevé.

Au niveau de l'accès aux traitements autorisés, certaines améliorations ont été réalisées dans le cadre du règlement de l'UE sur les orphelins. Les produits atteignent de plus en plus de patients et les atteignent plus rapidement.

Dans l'ensemble, le règlement de l'UE sur les orphelins a contribué à répondre à certains des besoins non satisfaits des patients atteints de maladies rares, mais les besoins non satisfaits restent considérables, tant en termes de disponibilité des traitements que d'accès.

Dans quelle mesure l'incitation (supplémentaire) au développement de la "médecine pédiatrique orpheline" s'est-elle traduite par de nouveaux médicaments répondant à un besoin médical non satisfait pour les enfants?

Chiffres clés

- 76% de toutes les désignations et 78% des produits autorisés sont destinés à des maladies qui affectent (également) les enfants.
- 55 (39%) médicaments orphelins autorisés ont été approuvés pour l'utilisation chez les enfants.
- 44 produits ont été autorisés pour les formes de cancer qui affectent (également) les enfants ; 13 d'entre eux sont approuvés pour une utilisation chez les enfants.

Un grand nombre de produits ont été autorisés pour des conditions touchant les adultes et les enfants. Cependant, moins de la moitié d'entre eux ont été approuvés pour l'utilisation chez les enfants. Cela donne à penser que le règlement n'a pas été suffisamment efficace pour contribuer à la mise sur le marché de produits destinés à ce groupe particulier. Bien que le manque de développement pour l'utilisation pédiatrique se manifeste dans tous les domaines thérapeutiques et toutes les indications, c'est dans le domaine de l'oncologie pédiatrique qu'il est le plus présent.

La plus grande raison invoquée par les développeurs pour (ne pas) mettre au point des traitements pour des maladies qui touchent principalement les enfants est liée à l'adéquation avec le portefeuille de R-D existant. D'autre part, le développement insuffisant des produits destinés à des indications pédiatriques,

dans le cas d'affections touchant à la fois les enfants et les adultes, a également été lié au fait qu'il n'est pas autorisé de détenir des indications orphelines et non orphelines sous une autorisation de mise sur le marché unique.

Les problèmes liés au développement des médicaments pédiatrique orphelins sont en partie liés à l'interaction entre le règlement de l'UE sur les médicaments orphelins et le règlement de l'UE sur les médicaments pédiatriques, comme examiné ci-après.

Dans quelle mesure le règlement orphelin et sa mise en œuvre ont-ils contribué à l'objectif général de compétitivité de l'industrie pharmaceutique européenne? Quels sont les facteurs qui ont favorisé ou entravé la réalisation de cet objectif?

Chiffres clés

- Il y a environ 1.000 entités uniques répertoriées en tant que promoteur
- 87 % de toutes les désignations et 100 % des autorisations sont détenues par des entreprises pharmaceutiques et biotechnologiques (y compris des PME).
- Les PME détiennent environ 40 % des désignations
- 53% des promoteurs ont leur siège dans l'UE/EEE
- Les désignations ont été transférées entre promoteurs 640 fois.
- Le transfert d'une promotion s'effectue dans la même mesure de et à l'UE/l'EEE.

Le règlement de l'UE sur les orphelins a renforcé le climat de la R&D pour les maladies rares, avec une augmentation marquée du nombre d'acteurs dans ce domaine, tant dans le monde universitaire que dans l'industrie.

Les entreprises pharmaceutiques et les PME détiennent la grande majorité de toutes les désignations et de toutes les autorisations de mise sur le marché. Néanmoins, des acteurs plus petits, tels que les établissements d'enseignement supérieur, jouent également un rôle, surtout aux premiers stades du processus de développement. Rien n'indique clairement que les entreprises basées dans l'UE/EEE jouent un rôle plus important dans certaines parties de l'écosystème que dans d'autres.

Étant donné que la R&D dans l'UE/EEE n'est pas obligatoire, le règlement n'a pas les moyens d'influencer directement la compétitivité de l'industrie. En fait, la prise de décision quant au lieu où les activités de R-D sont menées dépend en grande partie d'autres facteurs, comme la capacité de mener des essais cliniques, la présence de réseaux de recherche et la disponibilité de chercheurs, ainsi que les incitatifs économiques à la R-D (p. ex., les allègements fiscaux). Le règlement de l'UE sur les médicaments orphelins ne peut donc apporter qu'une contribution indirecte à la compétitivité de l'industrie pharmaceutique européenne, qui n'a pu être quantifiée.

Les dispositions du règlement sur les orphelins sont-elles suffisamment explicites quant au moment où l'exclusivité commerciale doit être accordée et révoquée?

Chiffres clés

- Aucun document n'est conservé sur les motifs de retrait volontaire de la désignation d'orphelin par les parrains.
- La réduction de l'exclusivité commerciale a été demandée une fois par un État membre ; l'EMA a toutefois constaté que les critères d'éligibilité restaient remplis.

L'octroi de l'exclusivité commerciale dépend de l'évaluation de la question de savoir si le produit remplit toujours tous les critères de désignation au moment de l'autorisation de mise sur le marché. Bien que les critères soient suffisamment explicites, les promoteurs ont parfois de la difficulté à les respecter, surtout lorsqu'il s'agit de démontrer des bénéfices suffisants du produit/traitement.

Les promoteurs indiquent qu'ils choisissent parfois de retirer leur désignation en raison des coûts associés au maintien d'autorisations de mise sur le marché distinctes pour les conditions orphelines et non orphelines.

Bien que le règlement contienne une disposition qui permettrait de réduire l'exclusivité commerciale à six ans au cas où les critères d'éligibilité ne seraient plus remplis, un tel cas ne s'est jamais produit dans la pratique. La non-application de cette disposition, et par conséquent son manque d'efficacité, est en effet liée à la manière dont elle a été formulée : la réévaluation ne peut se faire que sur la base des motifs de désignation d'origine. Par conséquent, la période d'exclusivité commerciale pour un produit désigné sur la base de la prévalence ne pourra pas être réduite sur la base des bénéfices réalisés.

Une deuxième raison pour la non-application de cette disposition est que la réévaluation des critères ne peut être demandée que par les États membres. Ces organismes ne disposent généralement pas des ressources et de l'information nécessaires pour vérifier si une demande de nouvelle cotisation est raisonnable. Ils ont donc fait valoir que la responsabilité pour ce processus devrait être transférée à l'EMA. Il est clair que, dans sa forme actuelle, le règlement est explicite, mais peu efficace pour ce qui est de prévoir la possibilité de révoquer l'exclusivité commerciale après qu'un produit a été autorisé.

Efficacité

Les coûts supportés par chaque partie prenante sont-ils raisonnables par rapport aux avantages (pour le groupe spécifique)? Y a-t-il une répartition équitable des coûts entre les principaux acteurs?

Chiffres clés

Notre évaluation des coûts et des avantages pour la société révèle une grande incertitude quant à la taille et à la répartition des coûts pour les parties prenantes qui est liée au règlement sur les orphelins en 2000-2017. L'analyse de référence donne les résultats suivants, mais elle doit être considérée comme indicative, car la disponibilité des données ne permet pas d'obtenir un niveau élevé de certitude :

- Les développeurs ont dépensé 11 milliards d'euros supplémentaires en R&D sur les médicaments orphelins à la suite du règlement de l'UE sur les médicaments orphelins.
- Les recettes des ventes supplémentaires tirées de l'autorisation des médicaments orphelins par l'UE correspondent dans une large mesure aux coûts supplémentaires de R&D et de production.
- Le chiffre d'affaires supplémentaire attribué à l'exclusivité commerciale s'élève à 5 milliards d'euros.
- Les coûts pour les systèmes de santé liés au traitement par des médicaments orphelins ont augmenté d'environ 20 à 25 milliards d'euros.
- Les dispenses de frais et l'aide au protocole sont évaluées à 0,2 milliard d'euros.
- Les gouvernements nationaux et l'UE ont contribué à hauteur de 0,8 milliard d'euros à la recherche sur les maladies rares.
- Pour 24 médicaments orphelins, le rapport coût-efficacité marginal moyen est de 110 000 euros, avec une moyenne pondérée de 54 000 euros par année de vie pondérée par la qualité.
- L'impact cumulé sur la santé des médicaments orphelins autorisés est estimé entre 200 000 et 410 000 années de vie pondérée par la qualité (2000-2017).

Pour les développeurs de médicaments orphelins, les coûts et recettes supplémentaires résultant du règlement de l'UE sur les médicaments orphelins sont, en moyenne, assez équilibrés, mais la marge d'incertitude est élevée.

Pour les systèmes de santé, l'effet net des surcoûts supplémentaires (liés au traitement avec les nouveaux médicaments) et des économies (résultant d'une réduction des maladies ou du fait que d'autres traitements ne sont plus utilisés) n'a pu être établi en raison d'un manque d'informations publiquement disponibles.

Les patients atteints de maladies rares en sont les principaux bénéficiaires, en raison de la réduction de la morbidité et de la mortalité et de l'amélioration de la qualité de vie. Il est probable que les patients, les soignants et d'autres personnes aient également bénéficié d'avantages économiques plus larges, tels que les répercussions sur les soins (informels), la productivité et la qualité de vie des proches. Toutefois, la taille de ces derniers n'a pas pu être établie au niveau du règlement de l'UE sur les orphelins, principalement en raison de la grande variation des conditions visées. Il s'agira néanmoins probablement d'une valeur positive, étant donné que les maladies rares sont souvent très invalidantes et représentent un lourd fardeau pour tous.

Les coûts sociétaux directement liés aux incitations du règlement de l'UE sur les orphelins (5 milliards d'euros pour l'exclusivité commerciale, 1 milliard d'euros pour d'autres incitations) sont bien inférieurs aux dépenses supplémentaires dues à l'amélioration de l'accessibilité des produits.

Les coûts sociétaux par QALY pour les médicaments orphelins autorisés dépassent souvent les valeurs indicatives de référence utilisées par certains gouvernements nationaux. Toutefois, alors que, selon les rapports d'ETS, de nombreux médicaments orphelins sont censés améliorer la santé à un coût élevé par QALY, ceux qui sont effectivement sur le marché et remboursés sont généralement plus rentables.

La question de savoir si cette répartition des coûts et des avantages est "équitable" est une question entièrement subjective, car elle dépend de la valeur que l'on accorde non seulement à une vie humaine individuelle, mais aussi des implications que cette évaluation a pour la société dans son ensemble. Par conséquent, la présente étude s'abstient de tirer des conclusions sur l'équité de la répartition, laissant aux décideurs politiques et au grand public le soin de le faire avec les données présentées ici en main.

Les objectifs du règlement relatif aux orphelins auraient-ils pu être atteints différemment, c'est-à-dire à moindre coût?

Chiffres clés

- Environ 10 à 12 % des désignations donnent lieu à un produit autorisé.
- 12 produits ont été autorisés pour deux ou plusieurs indications orphelines, dont 75% sont oncologiques.
- 77 % des produits autorisés sont de nouvelles substances actives ; 19 % sont des produits d'utilisation bien établie ou des substances actives connues.

Bien que les coûts administratifs liés à l'application du règlement de l'UE sur les orphelins soient relativement faibles, ils ne sont pas négligeables pour les parties concernées. Des économies modestes pourraient être réalisées si le processus d'évaluation des demandes pouvait être optimisé, par exemple en exigeant des demandeurs qu'ils soumettent des dossiers de données plus complets et de meilleure qualité que ce qui est actuellement le cas.

Un élément de coût beaucoup plus important est lié aux coûts de santé résultant du traitement des patients avec des médicaments orphelins. La récompense de l'exclusivité commerciale permet aux promoteurs de bénéficier d'une période plus longue pendant laquelle le produit est protégé de la concurrence et des prix plus élevés peuvent être réalisés. Des effets indésirables ou, du point de vue des coûts sociétaux, des inefficacités peuvent survenir dans des situations où la proportionnalité entre la récompense de l'exclusivité commerciale et les coûts de développement du produit est mise en cause.

Les produits qui ont été autorisés pour de multiples indications orphelines ont un plus grand nombre de patients et peuvent donc réaliser plus de chiffre d'affaires. En outre, des périodes consécutives d'exclusivité commerciale prolongent la période de protection et peuvent retarder la concurrence des génériques plus longtemps que souhaitable. La possibilité d'obtenir plusieurs indications orphelines et des périodes d'exclusivité commerciale pour un même produit, sans différenciation, augmente le risque de surcompensation.

Le risque d'un déséquilibre entre la récompense et le coût existe également pour les produits qui n'ont pas été développés en tant que nouvelles substances actives. Le cadre réglementaire actuel du règlement de l'UE sur les orphelins ne contient aucune disposition visant à garantir le caractère abordable et l'accessibilité des produits, même lorsque le promoteur n'a effectué aucun investissement important en R&D. Les demandes telles que celles pour des produits d'utilisation bien établis et des substances actives connues reçoivent la même récompense que les nouvelles substances actives.

La période d'exclusivité commerciale de 10 ans ne semble pas offrir une compensation déraisonnable pour un médicament orphelin par rapport aux médicaments non orphelins, compte tenu à la fois d'un potentiel de recettes inférieur et de coûts de R&D inférieurs. Toutefois, il existe un risque de surcompensation si le chiffre d'affaires annuel est nettement supérieur à 100 millions d'euros, ou en cas de faibles coûts de développement. En cas de multiples indications orphelines autorisées, un tel niveau peut être atteint plus facilement. Dans le cas de produits d'utilisation bien établis et de substances actives connues, une surcompensation peut se produire parce que les coûts de R&D peuvent être inférieurs à la moyenne.

En l'absence de bonnes estimations des coûts de R&D au niveau des produits, on ne peut pas dire à quelle fréquence il y a surcompensation. Ce qui est clair, c'est que des gains d'efficacité pourraient être réalisés si la récompense du marché était mieux liée aux prix des produits, aux ventes réalisées et aux coûts de R&D.

Un autre domaine qui contribuerait à améliorer le rapport coût-bénéfice du règlement de l'UE sur les orphelins concerne le résultat du règlement, c'est-à-dire l'impact sur la santé. Nous remarquons que pour de nombreux médicaments orphelins, les données sur le rapport coût-efficacité ne sont pas disponibles. Cela signifie que les décisions d'autoriser l'entrée de médicaments orphelins sur les marchés nationaux ne sont pas toujours fondées sur des observations de coût-efficacité. Si l'on disposait d'informations économiques plus complètes, cela pourrait aider les autorités à prendre des décisions plus éclairées.

Quelle est l'importance de la charge administrative que le règlement orphelin représente pour certaines parties prenantes par rapport à la situation avant son entrée en vigueur?

Chiffres clés

- Le règlement de l'UE sur les médicaments orphelins ne contient aucune exigence obligatoire pour les développeurs de médicaments orphelins. La demande de désignation orpheline est volontaire.
- Le COMP compte 28 membres représentant les États membres, 3 membres experts nommés par la CE et 3 représentants des patients.
- Les membres du COMP et leurs institutions d'origine ne sont pas rémunérés pour leur travail.
- Le COMP se réunit actuellement 1 fois par mois, pendant 3 jours.

Le règlement de l'UE sur les médicaments orphelins est un instrument volontaire qui n'impose aucune exigence aux développeurs de médicaments orphelins qui choisissent de ne pas utiliser le règlement. Il n'y a donc pas de véritable fardeau administratif pour ce groupe d'intervenants qui semblent généralement satisfaits du cadre réglementaire et de son application.

Le règlement impose une certaine charge administrative au niveau de l'ÉMÉ. Ces coûts sont relativement faibles, mais ils sont susceptibles d'augmenter à mesure que le nombre de demandes continue d'augmenter. La question de l'augmentation de la charge de travail affecte également les membres du COMP. Le fardeau administratif associé au travail effectué par les membres du COMP incombe en grande partie à leur institution d'origine, qui n'est pas rémunérée. Cette situation met le système à rude épreuve et pourrait nuire à sa viabilité à long terme.

Cohérence

Dans quelle mesure le règlement orphelin est-il cohérent et complémentaire avec d'autres interventions communautaires et nationales dans le domaine pharmaceutique?

Le règlement de l'UE sur les orphelins a des liens clairs avec le règlement pédiatrique (1901/2006/CE), le règlement sur les médicaments de thérapie innovante (n° 1394/2007/CE) et le règlement concernant les certificats complémentaires de protection pour les médicaments (469/2009/CE). Elle s'inscrit également dans le cadre général de la politique pharmaceutique de l'UE. Cette complémentarité est reconnue par les parties prenantes.

Cela ne signifie pas pour autant que les différentes réglementations et politiques fonctionnent toutes ensemble de manière optimale. L'interaction entre le règlement de l'UE sur les orphelins et le règlement pédiatrique en est la preuve la plus évidente. Il y a un manque de développement de traitements pour les enfants atteints de maladies rares. Apparemment, les deux règlements qui devraient s'appliquer à cette population (à savoir le règlement sur les médicaments orphelins et le règlement pédiatrique) n'offrent pas les incitations

nécessaires pour orienter le développement vers cet important domaine. De manière plus générale, il a été noté que le système réglementaire global pour les produits pharmaceutiques est assez complexe et qu'il bénéficierait d'une architecture plus holistique et rationalisée. La complexité est perçue, par exemple, dans l'utilisation de concepts apparemment similaires mais distincts (p. ex. avantages significatifs et valeur ajoutée) entre les règlements et dans la façon dont les différents processus d'évaluation sont organisés les uns par rapport aux autres.

Les parties prenantes, en particulier les autorités publiques nationales, se sont également inquiétées du fait que, pour certains médicaments orphelins, les promoteurs ont la possibilité de "basculer" entre les protections offertes par le règlement de l'UE sur les médicaments orphelins et le règlement pédiatrique (c'est-à-dire l'exclusivité commerciale pour les médicaments orphelins et l'extension du CPS pour les médicaments pédiatriques, respectivement). Cela crée une incertitude pour les fabricants de génériques quant à la durée exacte de la protection, ce qui peut retarder davantage l'entrée de la concurrence sur le marché.

Le règlement de l'UE sur les orphelins a joué un rôle important en encourageant la mise en œuvre de diverses initiatives communautaires complémentaires et non législatives. Le règlement de l'UE sur les médicaments orphelins crée le cadre politique nécessaire pour soutenir le développement des médicaments orphelins, tandis que d'autres actions de l'UE soutiennent l'infrastructure dans laquelle se déroule la R&D.

Il existe de bons liens entre l'EMA, d'une part, et les autorités sanitaires nationales et les agences d'évaluation des technologies de la santé, d'autre part. Ces parties sont alignées dans leurs objectifs de fournir aux patients atteints de maladies rares les traitements nécessaires, en reconnaissant le rôle joué dans ce domaine par l'industrie pharmaceutique. Toutefois, les parties prenantes de différents groupes d'intérêt (par exemple les promoteurs, les autorités publiques nationales, les associations de patients) ont exprimé leurs préoccupations quant au manque apparent de cohérence entre les politiques nationales en matière de prise de décision sur la tarification et le remboursement des médicaments orphelins, ce qui contribue aux variations dans l'accès dans l'UE/EEE. La proposition actuelle de la Commission concernant un règlement de l'UE sur l'évaluation des technologies de la santé, si elle est adoptée, pourrait constituer une prochaine étape nécessaire pour atteindre un niveau plus élevé de convergence dans les méthodes d'évaluation des technologies de la santé et une plus grande cohérence entre les procédures communautaires d'autorisation de mise sur le marché et les procédures nationales de remboursement des médicaments.

Dans quelle mesure les différents outils (incitations, procédures, assistance) prévus par le règlement orphelin fonctionnent-ils de manière cohérente?

Le règlement de l'UE sur les orphelins est cohérent en soi : il offre un ensemble d'incitations qui fonctionnent bien ensemble et qui sont pertinentes tant pour les petits que pour les grands promoteurs. Chacun des outils ou incitations qui font partie du règlement de l'UE sur les orphelins a ses propres objectifs et sa

propre valeur et répond à des besoins distincts tout au long du cycle de développement du produit.

Les divers comités de l'ÉMÉ coopèrent raisonnablement bien, bien qu'il y ait place à l'amélioration, par exemple en ce qui concerne l'harmonisation des processus internes de l'ÉMÉ.

Quels sont les liens entre les domaines des médicaments orphelins et pédiatriques? Dans quelle mesure, en pratique, y a-t-il chevauchement et comment cela a-t-il influencé les progrès thérapeutiques?

Étant donné qu'environ 50 % de toutes les maladies rares se manifestent dans l'enfance, il existe un besoin évident de développer des médicaments orphelins pour les indications pédiatriques. Il convient donc qu'il existe un lien explicite entre le règlement communautaire sur les médicaments orphelins et le règlement pédiatrique, sous la forme d'une prolongation de la période d'exclusivité commerciale pour les médicaments orphelins pour lesquels des investigations pédiatriques ont été réalisées. Néanmoins, notre analyse montre que seulement la moitié de tous les médicaments orphelins actuellement autorisés ont été approuvés pour une utilisation chez les enfants.

Comme indiqué précédemment, ce manque de développement de traitements pour les enfants atteints de maladies rares peut s'expliquer, du moins en partie, par le fait que - même ensemble - le règlement sur les orphelins et le règlement pédiatrique ne fournissent pas les stimuli nécessaires pour orienter les développeurs vers cet important domaine. L'interaction sous-optimale entre les règlements peut être observée, par exemple, dans la façon dont les conditions sont définies. Normalement, le cadre réglementaire de l'UE pour les orphelins visera à définir des conditions aussi larges que possible afin d'inclure toutes les indications thérapeutiques potentielles. La tendance est alors de considérer les populations adultes et pédiatriques ensemble. Toutefois, cette approche pourrait signifier que le produit n'est pas admissible à la désignation orpheline même si le sous-ensemble représenté par la seule population pédiatrique le serait. Ce n'est que si le sous-ensemble pédiatrique est approuvé en tant qu'indication orpheline que le règlement communautaire sur les médicaments orphelins peut fournir les incitations nécessaires (y compris l'extension de l'exclusivité commerciale à l'issue des investigations pédiatriques). Si tel n'est pas le cas, le règlement pédiatrique continue d'imposer la réalisation d'investigations pédiatriques et récompensera leur achèvement. Toutefois, il n'encourage ni ne récompense spécifiquement le développement réussi d'applications pédiatriques.

Lors de l'examen des dérogations aux investigations pédiatriques, des problèmes ont également été identifiés qui entravent le développement de médicaments pour les patients pédiatriques. C'est particulièrement vrai dans le domaine de l'oncologie.

Valeur ajoutée de l'UE

Quelle a été la valeur ajoutée résultant de l'intervention de l'UE avec le règlement orphelin par rapport à ce qui pourrait être réalisé au niveau international, national ou régional sans une telle intervention?

La valeur offerte par le règlement de l'UE sur les orphelins par rapport à d'autres règlements similaires dans d'autres juridictions, en particulier aux États-Unis, ainsi qu'au-delà des efforts déployés au niveau national est difficile à établir. La raison en est que cela exige de projeter une situation qui n'a pas eu lieu. Néanmoins, on a tenté d'estimer cette valeur ajoutée par rapport à une situation de référence sans le règlement et en établissant un lien avec la situation de référence avant 2000.

Cette étude montre que le règlement de l'UE sur les médicaments orphelins a contribué à l'augmentation du nombre de médicaments orphelins qui ont été développés et qui sont mis sur le marché dans l'UE. Bien que l'analyse elle-même repose sur un certain nombre d'hypothèses et que l'estimation fournie soit très incertaine, on estime que le règlement de l'UE sur les médicaments orphelins a conduit à la création d'environ 21 médicaments orphelins supplémentaires. Comme indiqué précédemment, cet impact s'est accompagné d'un accès un peu plus rapide aux marchés de l'UE et d'une légère augmentation du nombre de marchés de l'UE où les produits sont disponibles. Il est également constaté que le nombre de marchés de l'UE sur lesquels des médicaments orphelins sont disponibles augmente avec le temps. Si tous ces effets sont, en moyenne, positifs, il n'y a pas d'équité entre les États membres quant à la manière dont ces avantages ont été répartis.

Étant donné que les résultats reposent sur une analyse statistique et qu'il est impossible d'identifier des produits individuels qui pourraient être entièrement liés au règlement communautaire sur les médicaments orphelins, il n'est pas possible de déterminer quels groupes de patients ont bénéficié le plus directement du règlement communautaire sur les médicaments orphelins. La comparaison par rapport à la situation de référence ne montre pas de rupture de tendance majeure dans la répartition par domaine thérapeutique, bien que cette conclusion soit compliquée par le très faible nombre de produits dans certaines régions.

Dans l'ensemble, il est raisonnable d'affirmer que le règlement de l'UE sur les médicaments orphelins a permis d'apporter une réponse plus concertée et plus efficace au problème de la défaillance du marché dans le développement des médicaments orphelins que ce qui aurait été possible au niveau des seuls États membres individuels. Elle a également servi de catalyseur aux efforts déployés par les États membres dans le domaine des maladies rares et des médicaments orphelins. L'exclusivité commerciale offerte aux médicaments orphelins autorisés par l'UE a été identifiée comme l'une des principales incitations offertes par le règlement. Cela n'aurait pas été possible au niveau d'un seul État membre, car ça aurait entraîné des distorsions du marché intérieur.

Quelle est l'utilité des initiatives non législatives dans le domaine des maladies rares (registres, bases de données d'information/épidémiologiques, etc.) pour le bon fonctionnement du règlement orphelin?

Les efforts de l'UE en termes de coopération et de financement de la recherche sur les maladies rares et les médicaments orphelins ont apporté une valeur ajoutée substantielle. La Commission contribue à un large éventail d'initiatives non législatives. Ces initiatives offrent une valeur ajoutée en réunissant les parties prenantes et en regroupant l'expertise et les données. En tant que tels,

ils complètent le règlement de l'UE sur les médicaments orphelins en renforçant le domaine de la recherche sur les maladies rares et le développement des médicaments orphelins.

Observations finales

Cette étude montre que le règlement de l'UE sur les médicaments orphelins a contribué à d'importants progrès dans le domaine des maladies rares et du développement des médicaments orphelins. Depuis l'introduction du règlement, davantage de produits ont été mis sur le marché. Il existe également un portefeuille prometteur de produits en cours de développement, qui pourrait apporter une réelle valeur ajoutée aux patients pour lesquels il n'existe actuellement aucune option thérapeutique.

Les besoins et les problèmes auxquels le règlement de l'UE sur les orphelins a répondu existent toujours et, en tant que tels, les objectifs du règlement restent aussi importants aujourd'hui qu'ils l'étaient il y a près de deux décennies.

Malgré ces succès importants, cette étude a montré que les progrès n'ont pas été les mêmes dans tous les domaines. Le règlement de l'UE sur les orphelins a également produit certains effets involontaires qui n'étaient pas prévus en 2000 ou pour lesquels l'ampleur de leur impact ne pouvait être prévue. Il est donc opportun d'examiner divers aspects du cadre réglementaire des médicaments orphelins dans l'UE.

La présente étude n'a pas été chargée d'élaborer des recommandations ou de préparer des options politiques pour l'avenir du règlement de l'UE sur les orphelins. Au lieu de cela, l'accent a été mis sur la rétrospective, tout en identifiant les domaines de tension qui pourraient avoir un impact sur le règlement à l'avenir. Lorsque les parties prenantes ont proposé des recommandations ou des points spécifiques à prendre en considération, ceux-ci ont été inclus.

Zusammenfassung der Studie

Studienziele

Die vorliegende Studie ermöglicht eine umfassende gemeinsame Evaluierung der EU-Verordnung über Arzneimittel für seltene Leiden und der EU Kinderarzneimittelverordnung. Zu diesem Zweck wurden Informationen zu fünf Bewertungsdimensionen gesammelt: A) Relevanz, B) Effektivität, C) Effizienz, D) Kohärenz und E) EU-Mehrwert der EU-Verordnung über Arzneimittel für seltene Leiden. Ziel war es, faktenbasierte Informationen über die Ergebnisse und Auswirkungen der Verordnung zu sammeln und zu analysieren sowie Stakeholder-Perspektiven zu der Verordnung und ihrer Umsetzung zu sammeln.

Die Europäische Kommission hat den Auftragnehmer gebeten, auf 17 verschiedene Bewertungsfragen einzugehen, die mit den oben genannten Bewertungsdimensionen zusammenhängen. Die Fragen dienten als Grundlage für die nachstehende Analyse und Präsentation der wichtigsten Ergebnisse.

Methodologie

Die Studie basiert auf einer Vielzahl von Datenquellen; in einer Reihe von Interviews und Online-Umfragen wurden Primärdaten von ausgewählten Interessengruppen erhoben. Es wurde eine öffentliche Online-Umfrage durchgeführt, um einen Einblick in die Perspektive von Personen mit persönlichen Erfahrungen mit seltenen Krankheiten (Patienten und Pflegepersonal) sowie von Mitarbeitern im Gesundheitswesen zu erhalten. Unabhängig davon erhielt das Studienteam unaufgeforderte schriftliche Beiträge von Interessengruppen.

Für die Studie wurden mehrere sekundäre Datenanalysen durchgeführt. Zunächst wurde eine umfassende Bewertung der von Fachleuten rezensierten wissenschaftlichen Literatur und grauer Literatur durchgeführt, um die Ergebnisse zu kontextualisieren und Datenlücken zu schließen. Darüber hinaus wurde eine eingehende Analyse des Datenportfolios der EMA über alle designierten und autorisierten Arzneimittel für seltene Leiden durchgeführt.

Um eine gesellschaftliche Kosten(-Nutzwert)-Analyse zu ermöglichen und die ökonomische Relevanz der Marktexklusivität für bestimmte Arzneimittel für seltene Leiden in der EU abzuschätzen, wurden Daten zum Verkauf von Arzneimitteln für seltene Leiden in der Europäischen Union und dem Patentstatus von Produkten verwendet.

Die Situation vor 2000

Die Evaluierung verglich die Arzneimittellandschaft für seltene Leiden Ende 2017 mit jener vor Inkrafttreten der EU -Verordnung im Jahr 2000. Zu diesem Zeitpunkt war der Bereich der Arzneimittel zur Behandlung seltener Krankheiten in Europa durch ein niedriges Niveau der FuE-Tätigkeiten und einen großen, ungedeckten medizinischen Behandlungsbedarf bei Patienten mit seltenen Krankheiten gekennzeichnet. Je nach verwendeten Definitionen und Datensätzen, waren in der EU geschätzte 15 bis 70 Produkte für seltene Krankheiten auf dem Markt. Der Zugang zu den entsprechenden Produkten war sehr ungleich verteilt.

Solange sich kein klares Geschäftsmodell abzeichnete, zeigte die Pharmaindustrie jedoch wenig Interesse. Das Problem ergab sich vor allem aus der von den jeweiligen Krankheiten betroffenen geringen Patientenzahl; ein Umstand der Pharmaunternehmen dazu veranlasste, die hiermit verbundene technisch anspruchsvolle und kostspielige Entwicklung von innovativen Medikamenten als ein unsicheres Geschäftsmodell einzustufen. In Europa gab es einige, wenn auch begrenzte, positive Spill-Over-Effekte durch die zuvor umgesetzten Rechtsvorschriften zur Unterstützung der Entwicklung von Medikamenten für seltene Leiden in den USA und Japan. Jedoch führten die fragmentierten nationalen Regulierungssysteme in Europa und die geringe Bevölkerungs- bzw. Patientenzahl zu eher schwachen wirtschaftlichen Anreizen. Auch die Forschungsgemeinschaft konstatierte das sich hieraus ergebende Manko an Geschäftsaktivitäten im Bereich der seltenen Krankheiten.

Die Notwendigkeit einer EU-Verordnung bei offensichtlichem Marktversagen in diesem Bereich wurde von verschiedenen EU-Mitgliedstaaten als legitime und effiziente Reaktion auf die große Ungleichheit hinsichtlich der Sozialkosten und der Gesundheit hervorgehoben. Die individuellen Mitgliedstaaten verfügten über wesentlich weniger Kapazität und Rechtsspielraum, um effektiv zu handeln.

Die aufgezeigten Probleme trugen letztlich zur Schaffung der Verordnung (EG) Nr. 141/2000 über Arzneimittel für seltene Leiden bei, die 1999 offiziell verabschiedet wurde.

Die EU-Verordnung Nr. 141/2000 über seltene Leiden und der Rechtsrahmen

Die EU-Verordnung über Arzneimittel für seltene Leiden verfolgt nicht nur die gleichen übergeordneten Ziele wie der US Orphan Drug Act, sondern entspricht ihm auch in wesentlichen konzeptionellen Teilen. Die Verordnung bietet Produktentwicklern eine Reihe von finanziellen und anderen Anreizen, um Investitionen in die Entwicklung von Medikamenten für seltene Leiden zu fördern.

Um für Anreize in Frage zu kommen, sollte ein Produkt für die Diagnose, Prävention oder Behandlung einer lebensbedrohlichen oder chronisch schwächenden Erkrankung bestimmt sein, die entweder nicht mehr als fünf von zehntausend Menschen in der EU betrifft oder ohne Anreize anderweitig nicht wirtschaftlich tragbar wäre. Es sollte darüber hinaus nachgewiesen werden, dass es keine zufriedenstellende Alternative zu dem Produkt gibt oder dass das Produkt einen erheblichen Nutzen gegenüber anderen verfügbaren Produkten bietet. Alle Anträge werden von einem dafür geschaffenen Gremium, dem Ausschuss für Arzneimittel für seltene Leiden, geprüft.

Erfüllt ein Produkt, das als Medikament für seltene Leiden gekennzeichnet ist, zum Zeitpunkt der Genehmigung des Inverkehrbringens alle Anforderungen, so wird ihm in der EU ein Marktexklusivitätsrecht von zehn Jahren gewährt. In diesem Zeitraum wird es keine Marktzulassungen für andere Behandlungen der gleichen Krankheit geben, wenn sie als vergleichbar mit dem zuvor zugelassenen Produkt angesehen werden. Weitere Anreize umfassen Gebührenbefreiungen und den Zugang zu einer speziellen Form der wissenschaftlichen Beratung, der sogenannten Protokollunterstützung. Die EU-

Verordnung über Arzneimittel für seltene Leiden sieht auch die Möglichkeit vor, dass Mitgliedsländer und die EU zusätzliche Forschungs- und Entwicklungshilfen leisten. Das zentralisierte Verfahren für die Marktzulassung wurde einem Mandat unterstellt, um die Bildung eines einheitlichen Markts zu fördern.









Neben der EU-Verordnung über Arzneimittel für seltene Leiden wurden eine Reihe von Leitlinien, Vermerken und Ausführungsbestimmungen entwickelt, die zusammengenommen den Rechtsrahmen ausmachen.

Sachstand

Die europäische Lage hat sich in den 19 Jahren seit der Einführung der EU-Verordnung über Arzneimittel für seltene Leiden hinsichtlich des Bestands verfügbarer Medikamente für seltene Leiden und der Investitionshöhe in Forschung und Entwicklung im Bereich seltener Krankheiten verändert.

Auf der Grundlage von Daten über das von der EMA zur Verfügung gestellte Portfolio an designierten und zugelassenen Medikamenten für seltene Leiden und von Verkaufsdaten in der EU/EWR wurde eine umfassende Analyse der verschiedenen Leistungen, Ergebnisse und Auswirkungen der EU-Verordnung über Arzneimittel für seltene Leiden durchgeführt. Einige wichtige Statistiken wurden in Abbildung 1 zusammengefasst.

Abbildung 1 Übersicht über die wichtigsten Ergebnisse der EU-Verordnung über Arzneimittel für seltene Leiden (2000-2017)

	1.956 Kennzeichnungen für 698 einzigartige Indikationen
	142 Zugelassene Medikamente für seltene Leiden für 107 einzigartige Indikationen
	55 Arzneimittel für seltene Leiden, die für die Verwendung bei Kindern zugelassen sind.
	Kennzeichnungen und zugelassene Medikamente in fast allen wichtigen Therapiegebieten
	Etwa 1/3 der Kennzeichnungen für Erkrankungen mit Prävalenz <5 in 100.000 Fällen
	76% zugelassene Arzneimittel für seltene Leiden
	~1,000 Sponsoren, 96 Zulassungsinhaber
	168x Marktexklusivität gewährt, 1.272 Anfragen zur Protokollunterstützung

Seit dem Inkrafttreten der Verordnung hat sich das Tätigkeitsvolumen bei der Entwicklung neuer Therapien für seltene Krankheiten deutlich erhöht. Bis Ende 2017 waren 142 Arzneimittel für seltene Leiden zugelassen. Diese decken ein breites Spektrum an Erkrankungen und Indikationen ab, darunter viele sehr

seltene Krankheiten. Basierend auf Schätzungen der Krankheitsprävalenz und der Bevölkerungszahl in der EU wird geschätzt, dass maximal 6,3 Millionen Menschen von diesen Behandlungen profitieren werden. In Wirklichkeit zielen Medikamente für seltene Leiden jedoch auf Teilmengen solcher Patienten ab, die auf Faktoren wie Krankheitsstadium und -schwere, Alter oder das Vorhandensein bestimmter Genmutationen basieren. Daher ist die tatsächliche Patientenzahl zu einem gegebenen Zeitpunkt nur ein Teil davon.

Der Anstieg an neuen Behandlungen (die Patienten seit 2000 zur Verfügung stehen) ging einher mit einem beschleunigten Markteintritt von Produkten und der Zunahme an EU/EWR-Ländern, in denen Produkte vermarktet wurden. Die Verfügbarkeit von Behandlungen ist in der EU jedoch nach wie vor sehr ungleich verteilt. Darüber hinaus stellt der zunehmende Preisdruck Marktzugangsbarrieren dar.

Durch die zunehmende Anzahl an (Anträgen für) Ausweisungen von Medikamenten für seltene Leiden ist auch die Inanspruchnahme der durch die EU-Verordnung über Medikamente für seltene Leiden geschaffenen Anreize wesentlich angestiegen. Der Anreiz der Marktexklusivität wurde insgesamt 168 Mal gewährt, wobei 20 Produkte mehr als eine Marktexklusivitätsperiode erhielten (für 46 Indikationen).

Ein zunehmender Anteil der europäischen Pharma- und Biotechnologieunternehmen hat sich mit der Erforschung seltener Krankheiten und der Entwicklung von Medikamenten für seltene Leiden beschäftigt. Die EMA hat in den letzten 18 Jahren Anträge von rund 1.000 Sponsoren bearbeitet. Über 70 unter ihnen vermarkten ein in der EU zugelassenes Arzneimittel für seltene Leiden.

Die jährlichen Ausgaben des öffentlichen Sektors für die Forschung an seltenen Krankheiten sind im Laufe des Zeitraums gestiegen, und zwar von mehreren zehn Millionen Euro Ende der 90er Jahre auf mehrere hundert Millionen Euro jährlich im Jahr 2018.

Relevanz

Inwieweit haben sich die spezifischen Zielsetzungen, die der Einführung der Verordnung über Arzneimittel für seltene Leiden zugrunde liegen, als geeignet erwiesen, um die zuvor identifizierten Probleme zu lösen? Inwieweit wird der derzeitige Anwendungsbereich der Verordnung den tatsächlichen (unerfüllten) Bedürfnissen der Patienten gerecht? Inwiefern hat sich die Verordnung dem Thema der Kapitalrendite angenommen?

Eckdaten

- Etwa 50% der 105 analysierten Arzneimittel für seltene Leiden in der EU generieren einen durchschnittlichen Jahresumsatz von 10 Mio. € oder weniger; etwa 15% erzeugen einen Jahresumsatz von mehr als 100 Mio. €.
- Von 2000 bis 2017 wurde für 105 Arzneimittel für seltene Leiden ein Gesamtumsatz von 44,1 Milliarden Euro in der EU berechnet.
- Der Jahresumsatz mit Arzneimittelwirkstoffen für seltene Leiden stieg von 2,5 Milliarden Euro im Jahr 2008 auf 6,3 Milliarden Euro im Jahr 2016.
- 70% (74 von 105 analysierten Produkten) aller zugelassenen Arzneimittel für seltene Leiden waren zum Zeitpunkt ihrer Zulassung noch durch ein Primärpatent oder SPC geschützt.
- Die durchschnittliche Verlängerung der Schutzdauer, die die Marktexklusivität über den Patent- oder SPC-Schutz hinaus bietet, beträgt 3,4 Jahre.
- 12 Produkte wurden für mehr als eine Indikation seltener Leiden zugelassen. Für 10 wurden alle Indikationen gleichzeitig zugelassen.

Die konkreten Ziele der Verordnung waren darauf ausgerichtet dem zuvor identifizierten Problem eines offensichtlichen Marktversagens zu begegnen. Die Entscheidung, eine EU-Verordnung anstelle einer EU-Richtlinie in die Wege zu leiten, bedeutete, dass die Rechtsvorschriften sofort in allen Mitgliedstaaten anwendbar waren, wodurch Verzögerungen und Inkonsistenzen bei der Umsetzung vermieden wurden. Dies hat dazu beigetragen, einen einheitlichen (größeren) Markt für Arzneimittel für seltene Leiden zu schaffen.

Das mangelnde wirtschaftliche Interesse der Industrie an der Entwicklung von Arzneimitteln für seltene Krankheiten dürfte wesentlich dazu beigetragen haben, dass keine Medikamente für seltene Krankheiten entwickelt wurden, obwohl dies keineswegs der einzige Grund gewesen ist. Die Gewährung von Marktexklusivität war daher grundsätzlich eine angemessene Antwort auf das offensichtliche Marktversagen. Sie räumte den Entwicklern eine Verlängerung der Frist für die Amortisierung ihrer Investitionen ein bevor sie mit Konkurrenten rechnen mussten. Die Relevanz der Marktexklusivität variiert jedoch je nach Produkt erheblich. Für einige Produkte ist sie praktisch die einzige Form des Wettbewerbsschutzes, für andere hingegen kann sie wenig bis gar keinen zusätzlichen Schutz vor generischem Wettbewerb bieten.

Da berechtigterweise davon ausgegangen werden kann, dass die Marktexklusivität für eine Teilmenge von Produkten ein entscheidender Faktor

für die Fähigkeit und Bereitschaft eines Investors gewesen ist, das Produkt zu entwickeln und auf den Markt zu bringen, kommen wir zu dem Schluss, dass die Einführung eines Marktexklusivitätsanreizes eine wesentliche und geeignete Maßnahme war.

Auch heute scheinen wirtschaftliche Anreize, um die Entwicklung bestimmter Produkte zu fördern, immer noch relevant zu sein da immer noch geringe Umsätze verzeichnet werden.

Gleichzeitig ist es bemerkenswert, dass sich der Markt für Arzneimittel für seltene Leiden verändert hat und heute zahlreiche hochprofitable Medikamente umfasst.

Vor diesem Hintergrund ist es auffällig, dass Investoren bei der Beantragung von Kennzeichnungen für Medikamente für seltene Leiden und der Rechtfertigung notwendiger Investitionen fast nie damit argumentierten, eine unzureichende Rendite zu erwarten. Dies wirft die Frage auf, ob die Designationen für Medikamente für seltene Leiden derzeit nicht auch für Produkte gewährt werden, bei denen berechtigterweise mit hohen Investitionsrenditen gerechnet werden kann, nur weil sie Krankheiten betreffen, die im Rahmen des Rechtsrahmens für die EU-Verordnung über Medikamente für seltene Leiden als selten gelten.

Daher ist es angebracht und legitim zu prüfen, ob in bestimmten Bereichen und für einige Produkte weiterhin wirtschaftliche Anreize erforderlich sind, die mit öffentlichen Mitteln verbunden sind. Zur Verbesserung der allgemeinen Wirksamkeit und Effizienz der Verordnung können sich alternative oder zusätzliche Maßnahmen als relevanter erweisen.

Inwieweit sind die Bestimmungen noch ein geeignetes Mittel, um eines der Hauptziele der Verordnung zu erreichen, nämlich dass Patienten mit seltenen Krankheiten Zugang zur gleichen Qualität medizinischer Produkte haben wie andere Patienten innerhalb der EU? Inwieweit wurde ein äquivalenter Zugang aller EU-Mitgliedstaaten erreicht und, falls es Unterschiede gibt, welche Gründe können hierfür gefunden werden?

Eckdaten

- Vor 2000 gab es mindestens 70 Produkte mit der US-Bezeichnung ‚Medikament für seltene Leiden‘ („Orphan-Likes“) in mindestens einem EU-Markt.
- Es dauerte in der Regel 2 bis 3 Jahre, bis die Produkte nach der Zulassung im ersten EU12-Mitgliedstaat und nach drei Jahren in 3 bis 4 EU-12-Mitgliedstaaten erhältlich waren.
- Die Zahl der in mindestens einem EU-Mitgliedstaat auf dem Markt befindlichen Arzneimittel für seltene Leiden stieg von 48 im Jahr 2008 auf 129 im Jahr 2016.
- In der gesamten EU bestehen nach wie vor große Unterschiede in Bezug auf die Gesamtverfügbarkeit der Medikamente und auf ihre Markteinführungsdauer.

Seit der Einführung der EU-Verordnung über Arzneimittel für seltene Krankheiten hat sich die Anzahl der Behandlungen für Patienten mit seltenen Krankheiten auf dem Markt verbessert, da mehr Produkte verfügbar, schneller verfügbar und eine etwas höhere Anzahl von Märkten erreicht wurden. So kann konstatiert werden, dass sich die "Kluft" zwischen Patienten mit seltenen Krankheiten und Patienten mit häufigeren Krankheiten verringert hat. Dennoch besteht nach wie vor ein sehr großer medizinischer Bedarf, weil es für die große Mehrheit der seltenen Krankheiten keine Behandlungsmöglichkeiten gibt. Ein verbesserter Zugang zu Arzneimitteln für seltene Leiden wurde nicht in allen EU-Mitgliedstaaten gleichermaßen erreicht. Zwischen den Mitgliedstaaten bestehen nach wie vor sehr große Unterschiede in Bezug auf die Verfügbarkeit und die Markteinführungsdauer.

Unterschiede in den nationalen Genehmigungsverfahren scheinen keine wichtige Ursache für diese Abweichung gewesen zu sein, selbst bevor das zentralisierte Verfahren für die Genehmigung des Inverkehrbringens obligatorisch wurde (2004). Vielmehr beruht ein erheblicher Teil der beobachteten Ungleichmäßigkeiten auf unterschiedlichen nationalen politischen Maßnahmen und Entscheidungsprozessen.

Diese Beobachtungen zeigen, dass das Ziel der EU-Verordnung über Arzneimittel für seltene Leiden, nämlich das Problem der Verfügbarkeit von und des Zugangs zu Medikamenten für seltene Leiden zu lösen, noch nicht erreicht wurde und auch heute noch genauso relevant ist wie zum Zeitpunkt der Verordnungseinführung.

Da mehr Medikamente für seltene Leiden entwickelt werden, besteht die reale Gefahr, dass die Ungleichheiten beim Zugang zur Behandlung von Patienten mit seltenen Krankheiten zunehmen. Denn viele dieser Produkte sind sehr kostspielig und die Länder innerhalb der EU/EWR-Region unterscheiden sich wesentlich in ihrer Fähigkeit und Bereitschaft, Kosten zu tragen. Infolgedessen ignorieren die Zulassungsinhaber weitgehend kleinere und weniger attraktive Märkte. Gleichzeitig kann der zunehmende Preisdruck dazu führen, dass mehr Länder restriktive Erstattungsrichtlinien anwenden. Innerhalb der EU-Verordnung über Arzneimittel für seltene Leiden gibt es weder die Instrumente noch das Mandat, auf dieser Ebene einzugreifen.

Welche Entwicklungen in diesem Bereich (z.B. neuartige Therapien, personalisierte Medizin, wissenschaftliche Entwicklungen, Verwendung realer Daten, Nachhaltigkeit der nationalen Gesundheitssysteme) haben maßgebliche Auswirkungen auf die Relevanz und Zukunft der Verordnung?

Eckdaten

- Der Anteil der neuartigen Therapien ist im Zeitraum 2010-2017 stark angestiegen, auf rund 11-20% aller neuen Kennzeichnungen. Bis Ende 2017 wurden 4 neuartige Therapien mit der Kennzeichnung für seltene Leiden zugelassen.
- Die personalisierte Medizin kann unter anderem dazu beitragen, die Wirksamkeit von Behandlungen zu verbessern. Sie kann auch die Zahl der Produkte, die mit einer Kennzeichnung für seltene Leiden in Verkehr gebracht werden, erheblich erhöhen, indem sie die Schaffung von „Untergruppen für seltene Leiden“ bei häufiger auftretenden Krankheiten ermöglicht.
- Von den 63 in der EU zwischen 2000 und 2010 zugelassenen Medikamenten für seltene Leiden durchliefen nur 38 eine randomisierte klinische Studie, von denen ein Drittel weniger als 100 Patienten betraf.

Es gab eine Reihe wissenschaftlicher Entwicklungen, die die Entwicklung neuer Therapien für seltene Krankheiten dramatisch verändert haben oder das Potenzial dazu haben. Zu den bedeutendsten Entwicklungen gehören jene in den Bereichen neuartiger Therapien, der personalisierten Medizin und neuer Studienkonzepte.

Diese Entwicklungen hatten bereits oder werden sich meistens deutlich positiv auf die Anzahl der neuen Therapien für Patienten mit seltenen Krankheiten auswirken. Sie stellen jedoch auch Herausforderungen für den Rahmen und die Anwendung der EU-Verordnung für seltene Krankheiten dar. Ein spezifisches Spannungsfeld betrifft die Verwendung von Biomarkern zur Definition eines Krankheitsbildes oder einer gültigen Untermenge für die Designation für seltene Leiden. Es gibt die weitverbreitete Befürchtung, dass die personalisierte Medizin die Grenzen des derzeitigen Rechtsrahmens erweitern wird, indem sie neu definiert, was eine seltene Krankheit ausmacht, und hierdurch letztlich alle Erkrankungen als selten ausgewiesen werden könnten. Hier gibt es einen weitverbreiteten Konsens darüber, dass der derzeitige Rahmen nicht ausreichen wird, um den ausgewiesenen Herausforderungen zu begegnen.

Eine weitere Herausforderung ist die Verwendung neuartiger Versuchsdesigns. Jene werfen zunehmend die Frage danach auf, welche Evidenzgrundlagen Regulierungsbehörden und Experten für Technologiefolgenabschätzungen im Gesundheitswesen als vertretbare Grundlage für Entscheidungsbildungen wahrnehmen. Obwohl jene Versuchsdesigns den besten Weg bieten, um Informationen in einem so anspruchsvollen Forschungsfeld zu sammeln, erfordern sie gleichzeitig ein tiefergehendes Engagement zwischen Entwicklern einerseits und Regulierungsbehörden und nachgelagerten Entscheidungsträgern andererseits, um gegenseitige Erwartungen zu klären.

Effektivität

Wie haben Entwickler die spezifischen Anreize der Verordnung genutzt und worauf beruhten ihre Entscheidungen?

Eckdaten

- Marktexklusivität wurde 168 Mal gewährt.
- Protokollunterstützung wurde 1.272 Mal beantragt.
- Der ausgewiesene Wert der Entgeltminderungen betrug 115 Mio. €.

Die verschiedenen Anreize tragen alle zur Entwicklung neuer Therapien für seltene Krankheiten bei. Die Wirksamkeit von Anreizen variiert jedoch, basierend auf Faktoren wie der Erfahrung des Entwicklers, Markt- und Produkteigenschaften, dem Entwicklungsstand des Produkts und verschiedenen anderen Faktoren.

Der Anreiz der Marktexklusivität wird besonders dafür geschätzt, das Ertragspotenzial von Medikamenten für seltene Leiden zu verbessern und so finanzielle Hindernisse für die Produktentwicklung abzubauen. Als Anreiz ist sie für die Beteiligten am wertvollsten, die sich bereits am Ende des Entwicklungsprozesses befinden und am ehesten ein Produkt auf den Markt bringen werden. Die Möglichkeit der Marktexklusivität durch die Erlangung einer Produktauszeichnung für seltene Leiden, trägt ebenfalls dazu bei, Investoren zu gewinnen.

Der Anreiz der Protokollunterstützung wird am wertvollsten von Produktentwicklern befunden, die nur begrenzte Vorkenntnisse in der klinischen Entwicklungsphase eines Produkts vorweisen. Inwiefern der Anreiz effektiv zu verbesserten Erfolgsaussichten führt ist jedoch nicht erwiesen.

Gebührenermäßigungen und -erlasse sind besonders für kleine und mittlere Unternehmen (für die vollständig auf Gebühren verzichtet wird) und andere Parteien mit begrenzten finanziellen Ressourcen von Bedeutung. Für letztere können verbleibende Gebühren jedoch noch ein Hindernis darstellen.

Die Auswirkungen einzelner Anreize lassen sich nicht voneinander trennen, genauso wenig kann die Wirksamkeit der Anreize der EU-Verordnung über Arzneimittel für seltene Leiden von Anreizen getrennt betrachtet werden, die durch ähnliche Regelungen anderer Rechtssysteme, wie dem amerikanischen, geboten werden.

Inwieweit ist die Verordnung über Arzneimittel für seltene Leiden effektiv in der Lage ungedeckte medizinische Bedürfnisse anzugehen?

Eckdaten

- Es wurden Kennzeichnungen für Produkte in 14 Hauptbereichen des Anatomisch-Therapeutisch-Chemischen (ATC) Klassifizierungssystems vergeben; in 13 Bereichen wurden Produkte zugelassen.
- Der größte Anteil der Produkte (28% der Kennzeichnungen; 34% der zugelassenen Produkte) besteht aus Krebsmedikamenten; die stärkste Konzentration an Indikationen für seltene Leiden befindet sich ebenfalls bei Krebsformen.
- 698 einzigartige Indikationen für seltene Leiden wurden ausgewiesen; 107 Produkte mit Indikationen einzigartiger Leiden wurden zugelassen.
- Ab 2014 betrifft etwa jede fünfte Kennzeichnung eine neue Indikation für seltene Leiden.
- Für 72% der zugelassenen Produkte war ein Nachweis über einen erheblichen Nutzen des Produkts für diejenigen, die von diesem Leiden betroffen sind, erforderlich.
- Für 61% der einzigartigen Indikationen für seltene Leiden gibt es nur 1 Ausweisung.
- Für 82% der einzigartigen Indikationen für seltene Leiden wurde nur 1 Produkt zugelassen.
- Etwa ein Drittel der Produkte sind Behandlungen mit einer Prävalenz von weniger als 5 von 100.000 (30% der Kennzeichnungen, 35% der zugelassenen Produkte).

Die Auswirkungen der Verordnung werden von uns wie folgt bewertet:

- Im Zeitraum von 2000 bis 2017 wurden 21 zusätzliche Arzneimittel für seltene Leiden entwickelt und im EWR eingeführt.
- Die durchschnittliche Markteinführungszeit hat sich um durchschnittlich 9 Monate verringert.
- Medikamente für seltene Leiden sind drei Jahre nach der Markteinführung für durchschnittlich 2,7 % der Gesamtbevölkerung der EU (oder 14 Millionen Bürger) erhältlich.

Seit der Einführung der EU-Verordnung über Arzneimittel für seltene Leiden wurde einer großen Anzahl von Produkten die Ausweisung für seltene Leiden zuerkannt und die Anzahl der zugelassenen Behandlungen hat deutlich zugenommen. Diese neuen Produkte leisten einen sinnvollen Beitrag zur Deckung der bisher unerfüllten Bedürfnisse von Patienten mit seltenen Krankheiten, darunter viele mit sehr seltenen Erkrankungen. Was jedoch die Vermarktung von Behandlungen in Gebieten anbelangt, in denen es noch nie zuvor eine ähnliche oder keine Behandlung gab, so weist die Verordnung eine

sinkende Rendite auf: Heute ist nur noch etwa ein Viertel der neu in den Verkehr gebrachten Arzneimittel für Krankheiten bestimmt, für die es keine alternativen Behandlungsmöglichkeiten gibt, und weniger als jedes fünfte Arzneimittel wird für Krankheiten ausgewiesen, für die noch kein anderes Arzneimittel diesen Status erhalten hat.

Während zugelassene Produkte ein breites Spektrum von Bereichen und Indikationen abdecken, kann gleichzeitig insbesondere bei onkologischen Behandlungen eine gewisse Clusterbildung beobachtet werden. Dies wurde mit einer Reihe von Faktoren in Verbindung gebracht - darunter der Verfügbarkeit wissenschaftlicher Erkenntnisse, der Anpassung an bestehende F&E-Portfolios und der Verfügbarkeit anderer Behandlungsmöglichkeiten. Jedoch ist es wahrscheinlich kein Zufall, dass die Clusterbildung vor allem in Bereichen beobachtet wird, die eine eher erhöhte Kapitalrendite aufweisen.

Auf der Ebene des Zugangs zu bewilligten Behandlungen sind durch die EU-Verordnung über Arzneimittel für seltene Leiden einige Verbesserungen entstanden. Eine größere Anzahl an Patienten hat Zugriff auf Produkte und erhalten diese auch schneller.

Insgesamt hat die EU-Verordnung über Arzneimittel für seltene Leiden dazu beigetragen, einen Teil des unerfüllten Bedarfs von Patienten mit seltenen Erkrankungen zu decken. Aber es gibt nach wie vor einen erheblichen unerfüllten Bedarf, sowohl was die Verfügbarkeit von Behandlungen als auch den Zugang zu entsprechenden Produkten betrifft.

Inwieweit hat der (zusätzliche) Anreiz für die Entwicklung der "Kindermedizin für seltene Leiden" zu neuen Arzneimitteln geführt, die einen unerfüllten medizinischen Bedarf bei Kindern decken?

Eckdaten

- 76% aller Kennzeichnungen und 78% der zugelassenen Produkte sind für Konditionen bestimmt, die (auch) Kinder beeinträchtigen.
- 55 (39%) zugelassene Arzneimittel für seltene Leiden sind für die Verwendung bei Kindern zugelassen.
- 44 Produkte sind für Krebserkrankungen zugelassen, die (auch) Kinder beeinträchtigen; 13 davon sind für die Verwendung bei Kindern zugelassen.

Eine große Anzahl von Produkten wurde für Erkrankungen von Erwachsenen und Kindern zugelassen. Weniger als die Hälfte davon ist jedoch für die Verwendung bei Kindern zugelassen. Dies deutet darauf hin, dass die Verordnung nicht ausreichend dazu beigetragen hat, dass Produkte für diese spezielle Gruppe auf den Markt gelangen. Obwohl die unzureichende Entwicklung pädiatrischer Anwendungen über alle Therapiegebiete und Indikationen hinweg zu beobachten ist, ist sie vor allem im Bereich der pädiatrischen Onkologie zu verzeichnen.

Der Hauptgrund, aus dem Entwickler Behandlungen für Krankheiten, die vor allem Kinder beeinträchtigen, (nicht) entwickeln, hängt mit der Anpassung an bestehende F&E-Portfolios zusammen. Die unzureichende Entwicklung von

Produkten für pädiatrische Indikationen bei Erkrankungen, die sowohl Kinder als auch Erwachsene betreffen, hängt jedoch auch damit zusammen, dass es nicht erlaubt ist, Indikationen für seltene Leiden zusammen mit Indikationen, die nicht auf seltene Leiden zutreffen im Rahmen einer einzigen Zulassung zu führen.

Probleme bei der Entwicklung von pädiatrischen Medikamenten für seltene Leiden ergeben sich zum Teil aus dem Zusammenspiel zwischen der EU-Verordnung über Arzneimittel für seltene Leiden und der EU-Kinderarzneimittel-Verordnung, wie im Folgenden dargestellt werden soll.

Inwieweit hat die Verordnung über Arzneimittel für seltene Leiden und ihre Umsetzung zum allgemeinen Ziel der Wettbewerbsfähigkeit der europäischen Pharmaindustrie beigetragen? Welche Faktoren haben hierzu beigetragen und welche waren diesem Ziel hinderlich?

Eckdaten

- Es gibt ca. 1.000 einzelne Instanzen, die als Sponsoren aufgeführt sind.
- 87% aller Kennzeichnungen und 100% der Genehmigungen wurden an Pharma- und Biotechnologieunternehmen (einschließlich KMUs) vergeben.
- Auf KMUs entfallen ca. 40% der Kennzeichnungen.
- 53% der Sponsoren haben ihren Sitz in der EU/EWR-Region.
- Kennzeichnungen wurden 640 Mal zwischen Sponsoren übertragen.
- Übertragung der Förderung erfolgt in gleichem Maße von und auf die EU/EWR.

Die EU-Verordnung über Arzneimittel für seltene Krankheiten hat das Klima für Forschung und Entwicklung im Bereich seltener Krankheiten gestärkt, da die Zahl der Akteure vor Ort sowohl in der Wissenschaft als auch in der Industrie deutlich zugenommen hat.

Pharmaunternehmen und KMUs verfügen über die überwiegende Mehrheit aller Kennzeichnungen und Zulassungen. Jedoch spielen auch kleinere Akteure wie akademische Institutionen eine Rolle, meist in den frühen Phasen des Entwicklungsprozesses. Es gibt keine eindeutigen Hinweise darauf, dass EU/EWR-Unternehmen in manchen Teilen des Ökosystems eine bedeutendere Rolle spielen als in anderen.

Da die Durchführung von FuE-Tätigkeiten in der EU/EWR keine Bedingung darstellt, ist die Verordnung nicht im Stande, die Wettbewerbsfähigkeit der Industrie direkt zu beeinflussen. Tatsächlich hängt die Entscheidung dafür, an welchem Ort FuE-Aktivitäten durchgeführt werden, weitgehend von anderen Faktoren ab, wie der Fähigkeit zur Durchführung klinischer Studien, dem Vorhandensein von Forschungsnetzwerken und der Verfügbarkeit von Forschern sowie wirtschaftlichen FuE-Anreizen (z.B. Steuererleichterungen). Die EU-Verordnung über Arzneimittel für seltene Leiden kann daher nur indirekt zur Wettbewerbsfähigkeit der europäischen Pharmaindustrie beitragen, jedoch konnte dies nicht quantifiziert werden.

Wird durch die Bestimmungen der Verordnung über Arzneimittel für seltene Leiden hinreichend klar, in welchen Fällen Marktexklusivität gewährt bzw. widerrufen werden sollte?

Eckdaten

- Es liegen keine nachgewiesenen Ursachen für die freiwillige Widerrufung von Ausweisungen seltener Leiden durch Sponsoren vor.
- Die Einschränkung der Marktexklusivität wurde einmalig durch einen Mitgliedstaat beantragt; die EMA befand jedoch, dass die Zulassungskriterien weiterhin erfüllt waren.

Die Gewährung der Marktexklusivität hängt davon ab, ob das Produkt zum Zeitpunkt der Zulassung noch alle Designationskriterien erfüllt. Während die Kriterien hinreichend klar sind, kämpfen Sponsoren jedoch zuweilen damit, sie zu erfüllen, insbesondere wenn es um den Nachweis des erheblichen Nutzens eines Produkts oder einer Behandlung geht.

Sponsoren haben angemerkt, dass sie sich in manchen Fällen dafür entscheiden, die erhaltene Ausweisung zu widerrufen, und weisen dabei auf die Kosten hin, die mit der Aufrechterhaltung getrennter Zulassungen für seltene und nicht seltene Leiden verbunden sind.

Obwohl die Verordnung eine Bestimmung enthält, die es ermöglichen würde, die Marktexklusivität auf 6 Jahre zu reduzieren, falls die Zulassungskriterien nicht mehr erfüllt sind, wurde dies in der Praxis nie umgesetzt. Die fehlende Anwendung dieser Bestimmung und ihre damit einhergehende Unwirksamkeit hängt mit der Formulierung zusammen: Eine Neubewertung kann nur auf der Grundlage der ursprünglichen Bestimmungsgründe erfolgen. Folglich kann die Marktexklusivitätsfrist für ein Produkt, das auf der Grundlage der Prävalenz bestimmt wurde, nicht auf der Grundlage seines realisierten Gewinns verkürzt werden.

Ein zweiter Grund ist, dass die Neubewertung nur von den Mitgliedstaaten beantragt werden kann. Diese verfügen in der Regel nicht über die erforderlichen Ressourcen und Informationen, um zu überwachen, ob ein Antrag auf Neubewertung sinnvoll ist. Es wird daher argumentiert, die Verantwortung auf die EMA zu verlagern. Es wird deutlich, dass die Verordnung in ihrer jetzigen Form zwar explizit, aber nicht sehr effektiv ist, um die Marktexklusivität zu widerrufen nachdem ein Produkt zugelassen wurde.

Effizienz

Sind die Kosten, die von den einzelnen Interessengruppen getragen werden, im Verhältnis zu den Leistungen (für die jeweilige Gruppe) angemessen? Existiert eine gerechte Kostenverteilung zwischen den Hauptakteuren?

Eckdaten

Unsere Einschätzung über die gesellschaftlichen Kosten und Nutzen der Verordnung über Arzneimittel für seltene Leiden ist, dass diese im Zeitraum von 2000 bis 2017 zu großen Unsicherheiten hinsichtlich der Höhe und Verteilung von Kosten für die Interessengruppen geführt hat. Die Referenzanalyse liefert die folgenden Ergebnisse, sollte jedoch als unverbindlich erachtet werden, da die eingeschränkte Datenverfügbarkeit zu einem unzureichendem Maß an Gewissheit führt:

- Die Entwickler haben durch die EU-Verordnung für seltene Leiden 11 Milliarden Euro mehr für Forschung und Entwicklung im Bereich der Arzneimittel für seltene Leiden ausgegeben.
- Zusätzliche Verkaufserlöse durch EU-zugelassene Medikamente für seltene Leiden stehen weitgehend im Einklang mit den Mehrkosten für F&E und die Produktion.
- Der zusätzliche Umsatz, der auf die Marktexklusivität zurückzuführen ist, betrug 5 Milliarden Euro.
- Die Kosten für die Gesundheitssysteme durch die Behandlung mit Medikamenten für seltene Leiden sind um ca. 20-25 Milliarden Euro gestiegen.
- Gebührenbefreiungen und Protokollunterstützung führten zu Kosten von 0,2 Mrd. €.
- Die nationalen Regierungen und die EU haben 0,8 Milliarden Euro für die Erforschung seltener Krankheiten bereitgestellt.
- Für 24 Arzneimittel für seltene Leiden beträgt die durchschnittliche inkrementelle Kosteneffizienz 110.000 €, wobei der gewichtete Durchschnitt 54.000 € pro qualitätsadjustiertes Lebensjahr beträgt.
- Die kumulierten gesundheitlichen Auswirkungen von zugelassenen Medikamenten für seltene Leiden werden auf 200.000 bis 410.000 qualitätsadjustierte Lebensjahre (2000-2017) geschätzt.

Für Entwickler von Arzneimitteln für seltene Leiden sind die zusätzlichen Kosten und Einnahmen infolge der EU-Verordnung für seltene Leiden im Durchschnitt recht ausgewogen, jedoch ist die Unsicherheitsspanne hoch.

Für die Gesundheitssysteme konnte der Nettoeffekt zusätzlicher Kosten (durch die Behandlung mit neuen Medikamenten) und Kosteneinsparungen (durch einen Rückgang der Krankheit oder die Tatsache, dass andere Behandlungen nicht mehr verwendet werden) mangels öffentlich zugänglicher Informationen nicht festgestellt werden.

Patienten, die mit seltenen Krankheiten leben, sind die Hauptbegünstigten, da sie von einer geringeren Morbidität und Mortalität sowie einer verbesserten Lebensqualität profitieren. Es dürfte auch zu weiteren wirtschaftlichen Vorteilen

für Patienten, Pflegekräfte und andere Personen gekommen sein, wie z.B. zu Auswirkungen auf die (informelle) Pflege, die Produktivität und die Lebensqualität von Angehörigen. Der Umfang dieser Ergebnisse konnte jedoch nicht auf der Ebene der EU-Verordnung für seltene Leiden festgestellt werden, was vor allem auf die großen Unterschiede zwischen den behandelten Konditionen zurückzuführen ist. Es wird sich jedoch wahrscheinlich um einen positiven Wert handeln, da seltene Krankheiten oft sehr beeinträchtigend sind und eine schwere Belastung für alle darstellen.

Die gesellschaftlichen Kosten, die direkt mit den Anreizen der EU-Verordnung für seltene Leiden zusammenhängen (5 Mrd. € für Marktexklusivität, 1 Mrd. € für andere Anreize), sind aufgrund des verbesserten Zugangs zu Produkten wesentlich geringer als zusätzliche Ausgaben.

Die gesellschaftlichen Kosten pro QALY für zugelassene Medikamente für seltene Leiden übersteigen häufig die von einigen nationalen Regierungen verwendeten Richtwerte. Während jedoch nach HTA-Berichten von vielen Medikamenten für seltene Leiden erwartet wird, dass sie zu gesundheitlichen Verbesserungen bei gleichzeitig hohen Kosten pro QALY führen, sind diejenigen, die tatsächlich auf dem Markt und zurückerstattet sind, im Allgemeinen kostengünstiger.

Ob diese Verteilung von Kosten und Nutzen "fair" ist, ist eine völlig subjektive Angelegenheit, da sie davon abhängt, welchen Wert man nicht nur einem individuellen Menschenleben zuspricht, sondern auch davon, welche Auswirkungen eine solche Bewertung auf die Gesellschaft als Ganzes hat. Daher verzichtet diese Studie darauf, Schlussfolgerungen über die Fairness der Verteilung zu ziehen, und überlässt dies den politischen Entscheidungsträgern und der breiten Öffentlichkeit mit den hier vorliegenden Daten.

Hätten die Ziele der Verordnung über Arzneimittel für seltene Leiden anders, d.h. zu niedrigeren Kosten, erreicht werden können?

Eckdaten

- Ca. 10 bis 12% der Ausweisungen führen zu einem zugelassenen Produkt.
- 12 Produkte wurden für zwei oder mehr Indikationen für seltene Leiden zugelassen, von denen 75% onkologischer Natur sind.
- 77% der zugelassenen Produkte sind neue Wirkstoffe, 19% sind etablierte Verwendungsprodukte oder bekannte Wirkstoffe.

Obwohl die Verwaltungskosten für die Anwendung der EU-Verordnung über Arzneimittel für seltene Leiden vergleichsweise gering sind, sind sie für die beteiligten Akteure nicht unerheblich. Eine relativ geringe Kosteneinsparung könnte erzielt werden, wenn der Prozess der Antragsprüfung optimiert werden könnte, z.B. durch die Verpflichtung der Antragsteller, vollständigere und hochwertigere Datendossiers einzureichen, als dies derzeit der Fall ist.

Ein wesentlich größerer Kostenposten sind die Gesundheitsausgaben, die sich aus der Behandlung von Patienten mit Medikamenten für seltene Leiden

ergeben. Die Marktexklusivitätsprämie bietet Sponsoren die Möglichkeit, über einen längeren Zeitraum zu verfügen, in dem das Produkt vor Wettbewerb geschützt ist und höhere Preise erzielen kann. Es können unerwünschte Auswirkungen oder (aus gesellschaftlicher Kostenperspektive) Ineffizienzen in Situationen entstehen, in denen die Verhältnismäßigkeit zwischen der Marktexklusivitätsprämie und den Kosten der Produktentwicklung in Zweifel gerät.

Produkte, die für mehrere Indikationen seltener Leiden zugelassen sind, haben eine größere Patientenbasis und können so auch mehr Umsatz erzielen. Darüber hinaus verlängern aufeinander folgende Marktexklusivitätsperioden die Schutzdauer und könnten so möglicherweise den generischen Wettbewerb länger als wünschenswert verzögern. Die Möglichkeit, für ein einzelnes Produkt ohne Differenzierung mehrere Indikationen seltener Leiden und Marktexklusivitätsperioden zu erhalten, erhöht das Risiko einer Überkompensation.

Das Risiko eines mangelnden Gleichgewichts zwischen Ertrag und Kosten besteht auch bei Produkten, die nicht als neue Wirkstoffe entwickelt wurden. Der derzeitige Rechtsrahmen für die EU-Verordnung für seltene Leiden enthält keine Bestimmungen, die die Erschwinglichkeit und Zugänglichkeit von Produkten gewährleisten, selbst wenn der Sponsor keine wesentlichen FuE-Investitionen getätigt hat. Anwendungen wie z.B. für etablierte Anwendungsprodukte und bekannte Wirkstoffe erhalten die gleiche Prämie wie neue Wirkstoffe.

Die Marktexklusivitätsfrist von 10 Jahren scheint keine unangemessene Kompensation für ein Medikament für seltene Leiden im Vergleich zu anderen Medikamenten zu bieten, wenn man sowohl das geringere Umsatzpotenzial als auch niedrigere F&E-Kosten berücksichtigt. Es besteht jedoch das Risiko einer Überkompensation, wenn der Jahresumsatz deutlich über 100 Mio. € liegt, oder auch im Fall von niedrigen Entwicklungskosten. Bei mehreren zugelassenen Indikationen seltener Leiden kann ein solches Niveau leichter erreicht werden. Bei etablierten Anwendungsprodukten und bekannten Wirkstoffen kann es zu Überkompensationen kommen, da die F&E-Kosten unterdurchschnittlich sein können.

Da keine guten Schätzungen der F&E-Kosten auf Produktebene vorliegen, kann nicht gesagt werden, wie oft eine Überkompensation stattfindet. Klar ist, dass Effizienzsteigerungen realisiert werden könnten, wenn der Marktnutzen besser mit Produktpreisen, realisierten Verkaufs- und F&E-Kosten in Beziehung gesetzt würde.

Ein weiterer Bereich, der zur Verbesserung des Kosten-Nutzen-Verhältnisses der EU-Verordnung über Arzneimittel für seltene Leiden beitragen würde, betrifft die Auswirkung der Verordnung, d.h. die gesundheitlichen Auswirkungen. Wir stellen fest, dass für viele Arzneimittel für seltene Leiden keine Kosteneffizienzdaten verfügbar sind. Dies bedeutet, dass Entscheidungen über den Eintritt von Medikamenten für seltene Leiden in nationale Märkte nicht immer auf Kosten-Nutzen-Analysen beruhen können. Wenn umfassendere ökonomische Angaben verfügbar wären, könnten diese auch zu einer besser informierten Entscheidungsfindung der Behörden beitragen.

Wie hoch ist der durch die Verordnung über Arzneimittel für seltene Leiden verursachte Verwaltungsaufwand für bestimmte Interessengruppen im Vergleich zu der Situation vor ihrem Inkrafttreten?

Eckdaten

- Die EU-Verordnung über Arzneimittel für seltene Leiden enthält keine verbindlichen Anforderungen an die Entwickler von Medikamenten für seltene Leiden. Die Beantragung der Designation für seltene Leiden ist freiwillig.
- Die COMP hat 28 Mitglieder, die die Mitgliedstaaten vertreten, 3 von der EG benannte Experten und 3 Patientenvertreter.
- COMP-Mitglieder und ihre Herkunftseinrichtungen erhalten keine Vergütung für ihre Arbeit.
- Das COMP trifft sich derzeit 1x pro Monat, für 3 Tage.

Die EU-Verordnung über Arzneimittel für seltene Leiden ist ein freiwilliges Instrument, das keine Anforderungen an die Entwickler von Medizin für seltene Leiden stellt, die sich dafür entscheiden, die Verordnung nicht in Anspruch zu nehmen. Somit gibt es keinen wirklichen Verwaltungsaufwand für diese Gruppe von Interessenvertretern, die generell mit dem Rechtsrahmen und seiner Anwendung zufrieden zu sein scheinen.

Auf der Ebene der EMA ergibt sich durch die Verordnung ein gewisser Verwaltungsaufwand. Die Kosten sind relativ gering, werden aber mit zunehmender Antragszahl voraussichtlich steigen. Das Problem einer zunehmenden Arbeitsbelastung betrifft auch die Mitglieder der COMP. Der mit der Arbeit der COMP-Mitglieder verbundene Verwaltungsaufwand entfällt weitgehend auf ihre Heimatinstitutionen, die hierfür nicht entschädigt werden. Dies stellt eine erhebliche Belastung für das System dar und könnte seine langfristige Tragfähigkeit beeinträchtigen.

Kohärenz

Inwieweit ist die Verordnung über Arzneimittel für seltene Leiden kohärent hinsichtlich bzw. ergänzend zu anderen EU- und nationalen Maßnahmen im Arzneimittelbereich?

Die EU-Verordnung über Arzneimittel für seltene Leiden steht in klarem Zusammenhang mit der Kinderarzneimittelverordnung (1901/2006/EG), der Verordnung über Arzneimittel für neuartige Therapien (Nr. 1394/2007/EG) und der Verordnung über ergänzende Schutzzertifikate für Arzneimittel (469/2009/EG). Sie fügt sich auch in den übergreifenden Rahmen der EU-Pharmapolitik ein. Diese Komplementarität wird von den Beteiligten anerkannt.

Dies bedeutet jedoch nicht, dass die verschiedenen Vorschriften und Richtlinien eine optimale Wirkungsübereinstimmung zusammen vorweisen können. Dieser Umstand wird am deutlichsten bei dem Zusammenspiel zwischen der EU-Verordnung über Arzneimittel für seltene Leiden und der Kinderarzneimittelverordnung. Die Entwicklung von Behandlungen für Kinder

mit seltenen Krankheiten ist mangelhaft. Offensichtlich bieten die beiden Verordnungen, die für diese Patientengruppe gelten sollen (nämlich die EU-Verordnung über Arzneimittel für seltene Leiden und der Kinderarzneimittelverordnung), nicht die notwendigen Anreize, um die Entwicklung auf diesen wichtigen Bereich auszuweiten. Generell wurde festgestellt, dass das gesamte Regulierungssystem für pharmazeutische Produkte recht komplex ist und von einer ganzheitlicheren und rationaleren Architektur profitieren würde. Die Komplexität zeigt sich zum Beispiel in der Verwendung scheinbar ähnlicher, aber dennoch unterschiedlicher Konzepte (z.B. signifikanter Nutzen und Mehrwert) zwischen den Regelungen und in der Organisation verschiedener Bewertungsverfahren zueinander.

Interessenvertreter insbesondere der nationalen Behörden äußerten sich auch besorgt darüber, dass die Sponsoren bei einigen Arzneimitteln für seltene Leiden die Möglichkeit haben, zwischen den Schutzmaßnahmen der EU-Verordnung über Arzneimittel für seltene Leiden und der Kinderarzneimittelverordnung (d.h. der Marktexklusivität für Produkte/Behandlungen für seltene Leiden und der Verlängerung der SPC für Kinderarzneimittel) zu wechseln. Dies schafft für die Generikahersteller Unsicherheit über die genaue Schutzdauer, was den Eintritt des Wettbewerbs in den Markt weiter verzögern kann.

Die EU-Verordnung für seltene Leiden hat eine wichtige Rolle bei der Förderung der Umsetzung verschiedener ergänzender, nicht legislativer EU-Initiativen gespielt. Die EU-Verordnung für seltene Krankheiten schafft den politischen Rahmen für die Förderung der Entwicklung von Arzneimitteln für seltene Leiden, während andere EU-Maßnahmen wiederum die Infrastruktur unterstützen, in der die Forschung und Entwicklung stattfindet.

Es bestehen gute Verbindungen zwischen der EMA auf der einen Seite und den nationalen Gesundheitsbehörden und den Agenturen für die Bewertung von Gesundheitstechnologien auf der anderen Seite. Diese Parteien sind in ihren Zielen darauf ausgerichtet, Patienten mit seltenen Krankheiten die notwendigen Behandlungen zur Verfügung zu stellen und erkennen die Rolle der Pharmaindustrie an. Parteien aus verschiedenen Interessengruppen (z.B. Sponsoren, nationale Behörden, Patientenorganisationen) haben jedoch ihre Besorgnis über die offensichtliche mangelnde Kohärenz zwischen den nationalen Verfahren zur Entscheidungsfindung über die Preisgestaltung und Erstattung von Medikamenten für seltene Leiden zum Ausdruck gebracht, was zu unterschiedlichen Zugangsmöglichkeiten innerhalb der EU/EWR beiträgt. Der aktuelle Vorschlag der Kommission für eine EU-Verordnung über die Bewertung von Gesundheitstechnologien könnte, falls er angenommen wird, ein notwendiger nächster Schritt sein, um ein höheres Maß an Konvergenz bei den Methoden der Bewertung von Gesundheitstechnologien und eine größere Kohärenz zwischen den EU-Verfahren für die Genehmigung des Inverkehrbringens und den nationalen Verfahren zur Erstattung von Arzneimitteln zu erreichen.

Inwieweit arbeiten die verschiedenen Instrumente (Anreize, Verfahren, Unterstützung), so wie sie in der Verordnung über Arzneimittel für seltene Leiden festgelegt sind, kohärent zusammen?

Die EU-Verordnung für seltene Leiden ist in sich kohärent: Sie bietet eine Reihe von Anreizen, die gut zusammenwirken und sowohl für kleinere als auch für größere Entwickler von Bedeutung sind. Jedes der Instrumente oder Anreize, die Teil der EU-Verordnung für seltene Krankheiten sind, hat seine eigenen Ziele und Werte und berücksichtigt unterschiedliche Bedürfnisse über den gesamten Lebenszyklus der Produktentwicklung hinweg.

Die verschiedenen EMA-Komitees arbeiten relativ gut zusammen, obwohl Verbesserungspotenzial besteht, z.B. bei der Ausrichtung der internen Prozesse innerhalb der EMA.

Welche Verbindungen gibt es zwischen den Bereichen Arzneimittel für seltene Leiden und Kinderarzneimittel? Inwieweit gibt es Überschneidungen in der Praxis und wie hat dies den therapeutischen Fortschritt beeinflusst?

Da etwa 50% aller seltenen Krankheiten im Kindesalter auftreten, besteht ein klarer Bedarf an der Entwicklung von Medikamenten für seltene Leiden mit pädiatrischen Indikationen. Daher ist es zweckmäßig, dass es einen ausdrücklichen Zusammenhang zwischen der EU-Verordnung für seltene Krankheiten und der Kinderarzneimittelverordnung gibt, und zwar in Form einer Verlängerung des Zeitraums der Marktexklusivität für Arzneimittel für seltene Leiden, für die pädiatrische Untersuchungen abgeschlossen wurden. Dennoch zeigt unsere Analyse, dass nur die Hälfte aller derzeit zugelassenen Medikamente für seltene Leiden für die Anwendung bei Kindern zugelassen sind.

Wie bereits erwähnt, kann die mangelnde Entwicklung von Behandlungen für Kinder mit seltenen Krankheiten zumindest teilweise darauf zurückgeführt werden, dass die Verordnung über Arzneimittel für seltene Krankheiten und die Kinderarzneimittelverordnung - auch gemeinsam - nicht die notwendigen Impulse geben, um Entwickler auf diesen wichtigen Bereich hin zu steuern. Das suboptimale Zusammenspiel der Verordnungen zeigt sich zum Beispiel in der Definition der medizinischen Leiden. Normalerweise zielt der EU-Rahmen für die Verordnung über Arzneimittel für seltene Leiden darauf ab, Leiden so weit wie möglich zu definieren, um alle möglichen therapeutischen Indikationen zu erfassen. Dadurch entsteht die Tendenz, erwachsene und pädiatrische Patientengruppen gemeinsam zu betrachten. Dieser Ansatz könnte jedoch bedeuten, dass ein Produkt nicht für die Designation für seltene Leiden in Frage kommt, obwohl dies für eine Teilmenge, also der pädiatrischen Teilmenge alleine, durchaus der Fall wäre. Nur wenn die pädiatrische Teilmenge als Indikation genehmigt wird, kann die EU-Verordnung die notwendigen Anreize bieten (einschließlich der Ausweitung der Marktexklusivität nach Abschluss der pädiatrischen Untersuchungen). Geschieht dies nicht, schreibt die Kinderarzneimittelverordnung dennoch die Durchführung pädiatrischer Untersuchungen vor und bezahlt deren Abschluss. Es werden jedoch keine spezifischen Anreize für eine erfolgreiche Entwicklung der pädiatrischen Anwendung gegeben oder prämiert.

Bei der Prüfung von Ausnahmeregelungen bei pädiatrischen Untersuchungen wurden auch Probleme identifiziert, die die Entwicklung von Medikamenten für pädiatrische Patienten behindern. Dies gilt insbesondere im Bereich der Onkologie.

Inwieweit ist der Begriff der Kennzeichnung mit der Vertriebsgenehmigung selbst vereinbar?

Es existiert ein gewisses Maß an Inkonsistenz zwischen den Konzepten der Designation für seltene Leiden und der Zulassung von Medikamenten für seltene Leiden. Zum einen wird nur ein kleiner Teil der Bezeichnungen schließlich in zugelassene Produkte umgewandelt. Dies kann zu dem unangenehmen Effekt führen, dass es zu übermäßigen Erwartungen kommt von Patienten mit Erkrankungen, für die die Produkte zwar bestimmt sind, die aber nicht erfolgreich entwickelt wurden. Dies unterscheidet sich jedoch nicht von anderen Bereichen der Produktentwicklung.

Ein gewisses Maß an Inkonsistenz besteht jedoch auch zwischen der Anwendung der Konzepte Indikation für seltene Leiden, die für Kennzeichnung verwendet wird, und der therapeutischen Indikation, die beschreibt, für wen eine zugelassene Behandlung verwendet werden kann. Aber auch hier ist nicht klar, ob es sich um ein ernsthaftes Problem handelt oder ob die Problematik nicht auch leicht zu vermeiden wäre.

EU-Mehrwert

Welchen Mehrwert hat die EU-Intervention der Verordnung über Arzneimittel für seltene Leiden im Vergleich zu dem, was auf internationaler, nationaler oder regionaler Ebene ohne eine solche Intervention erreicht werden könnte, erbracht?

Der Wert, den die EU-Verordnung über Arzneimittel für seltene Leiden über ähnliche Vorschriften in anderen Rechtsordnungen, insbesondere in den USA, hinaus sowie über die nationalen Bemühungen hinaus bietet, ist schwer nachzuweisen. Der Grund hierfür ist, dass dies erfordern würde, eine Situation zu prognostizieren, die nicht stattgefunden hat. Dennoch wurde versucht, den Mehrwert gegenüber einer Vergleichssituation ohne die Verordnung und durch einen Vergleich mit der Ausgangssituation vor 2000 abzuschätzen.

Die Studie stellt fest, dass die EU-Verordnung über Arzneimittel für seltene Leiden zu einem zahlenmäßigen Anstieg an entwickelten und in der EU auf den Markt gebrachten Arzneimittel für seltene Leiden beigetragen hat. Während die Analyse selbst auf einer Reihe von Annahmen beruht und die Schätzung mit erheblichen Unsicherheiten behaftet ist, wird angenommen, dass die EU-Verordnung für seltene Krankheiten zu etwa 21 zusätzlichen Medikamenten für seltene Leiden geführt hat. Wie bereits erwähnt, ist dieses Ergebnis parallel zu einem etwas schnelleren EU-Marktzugang und einem geringen zahlenmäßigen Anstieg der EU-Märkte, auf denen Produkte erhältlich sind, zu verzeichnen. Es wurde auch festgestellt, dass die Zahl der EU-Märkte, auf denen Arzneimittel für seltene Leiden erhältlich sind, mit der Zeit zunimmt. Obwohl alle diese Effekte im Durchschnitt positiv sind, gibt es zwischen den Mitgliedstaaten keine gleiche Verteilung der durch sie entstandenen Vorteile.

Da die Ergebnisse auf statistischen Analysen beruhen und es unmöglich ist, einzelne Produkte zu identifizieren, die ausnahmslos mit der EU-Verordnung über Arzneimittel für seltene Leiden zusammenhängen, ist es auch nicht möglich festzustellen, welche Patientengruppen am unmittelbarsten von der EU-Verordnung für seltene Leiden profitiert haben. Ein Vergleich mit der Ausgangssituation zeigt, dass es keine wesentlichen Trenddurchbrüche bei der Verteilung gibt (über alle Therapiegebiete hinweg), wobei eine solche Schlussfolgerung, durch die in einigen Bereichen sehr geringe Anzahl von Produkten erschwert wird.

Insgesamt lässt sich sagen, dass die EU-Verordnung über Arzneimittel für seltene Leiden eine konzertiertere und wirksamere Antwort auf die Herausforderung des Marktversagens bei der Entwicklung von Medikamenten für seltene Leiden ermöglicht hat, als dies allein auf der Ebene der einzelnen Mitgliedstaaten möglich gewesen wäre. Sie hat auch als Katalysator für die Bemühungen der Mitgliedstaaten im Bereich seltener Krankheiten und seltener Medikamente gewirkt. Die Marktexklusivität für EU-zugelassene Medikamente für seltene Leiden wurde als einer der wichtigsten Anreize der Verordnung identifiziert. Ein solcher Anreiz wäre auf der Ebene eines einzelnen Mitgliedstaates nicht möglich gewesen, da er zu Verzerrungen des Binnenmarkts geführt hätte.

Welchen Wert haben nichtlegislative Initiativen im Bereich der seltenen Krankheiten (Register, Informations-/Epidemiologische Datenbanken usw.) für das reibungslose Funktionieren der Verordnung über Arzneimittel für seltene Leiden?

Die Bemühungen der EU im Bereich der Zusammenarbeit und der Forschungsfinanzierung für seltene Krankheiten und Medikamente für seltene Leiden haben einen erheblichen Mehrwert erbracht. Die Kommission trägt zu einer Vielzahl von nichtlegislativen Initiativen bei. Diese Initiativen bieten einen Mehrwert, indem sie Interessengruppen zusammenbringen und Fachwissen und Daten bündeln. Als solche ergänzen sie die EU-Verordnung für seltene Krankheiten, indem sie den Bereich der Forschung zu seltenen Krankheiten und der Entwicklung von Arzneimitteln für seltene Krankheiten stärken.

Schlussbemerkungen

Diese Studie stellt fest, dass die EU-Verordnung über Arzneimittel für seltene Krankheiten zu wichtigen Fortschritten auf dem Gebiet der seltenen Krankheiten und der Entwicklung von Medikamenten für seltene Leiden beigetragen hat. Seit der Einführung der Verordnung sind mehr Produkte auf den Markt gekommen. Darüber hinaus gibt es eine aussichtsreiche Pipeline an sich in der Entwicklung befindenden Produkten, die einen realen Mehrwert für Patienten bedeuten können, für die derzeit keine Behandlungsmöglichkeit existiert.

Die Bedürfnisse und Probleme, auf die die EU-Verordnung über Arzneimittel für seltene Leiden reagiert hat, sind nach wie vor vorhanden, und als solche sind die Ziele der Verordnung auch heute noch so relevant wie vor fast zwei Jahrzehnten.

Ungeachtet dieser wichtigen Erfolge hat die hier vorliegende Studie gezeigt, dass Fortschritt nicht über alle Bereiche hinweg gleichmäßig erreicht wurde. Die EU-

Verordnung über Arzneimittel für seltene Leiden hat auch einige unbeabsichtigte Auswirkungen nach sich gezogen, die im Jahr 2000 entweder nicht vorhersehbar waren oder deren Wirkungsausmaß nicht vorhergesagt werden konnte. Daher ist es an der Zeit, verschiedene Aspekte des Rechtsrahmens für Arzneimittel für seltene Leiden in der EU zu prüfen.

Die vorliegende Studie war nicht damit beauftragt, Empfehlungen auszuarbeiten oder politische Optionen für die Zukunft der EU-Verordnung über Arzneimittel für seltene Leiden auszuarbeiten. Stattdessen konzentrierte sie sich auf die Retrospektive und identifizierte Spannungsfelder, die sich in Zukunft auf die Verordnung auswirken könnten. Sofern Interessengruppen spezifische Empfehlungen oder zu überprüfende Punkte vorlegten, wurden diese in den Bericht aufgenommen.

List of abbreviations

Abbreviation	Explanation
ATC	Anatomical Therapeutic Chemical classification system
ATMP	Advanced Therapy Medicinal Product
CAT	Committee for Advanced Therapies
CBA	Cost-benefit assessment
CHMP	Committee for Human Medicinal Products
COMP	Committee for Orphan Medicinal Products
DG RTD	Directorate-General for Research and Innovation
DG SANTE	Directorate-General for Health and Food Safety
EC	European Commission
EEA	European Economic Area
EMA	European Medicines Agency
ERN	European Reference Networks
EU	European Union
EURORDIS	European Organisation for Rare Diseases
FDA	US Food and Drug Administration
FP	Framework programme for research and technological development
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
IRDiRC	International Rare Diseases Research Consortium
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
ODA	US Orphan Drug Act

Study to support the evaluation of the EU Orphan Regulation

Abbreviation	Explanation
OMP	Orphan Medicinal Product
PDCO	Paediatric Committee
PDMA	Pharmaceuticals and Medical Devices Agency (Japan)
PIP	Paediatric Investigation Plan
R&D	Research and Development
RD	Rare diseases
RCT	Randomised Clinical Trial
RfS	Request for Services
RoI	Return on Investment
RWD	Real-World Data
SAWP	Scientific Advice Working Party
SME	Small and Medium-sized Enterprise
SmPC	Summary of Product Characteristics
SPC	Supplementary Protection Certificate
US	United States of America

About this report

This report is the final report for the study to support the evaluation of the EU Orphan Regulation. It focuses on the analysis and interpretation of the data collected in the period April 2018 through to January 2019.

The Report has been divided into the following main Sections:

Chapter 1 provides the background to the study, detailed objectives and evaluation questions. Furthermore, it outlines the methodologies used and discusses the study limitations.

Chapter 2 presents the landscape for orphan medicines prior to the introduction of the EU Orphan Regulation and can be interpreted as a baseline to this study.

Chapters 3 reviews why the EU Orphan Regulation was introduced, what objectives it has, and how it was designed. It includes a comparison to similar legislative initiatives in the US and Japan.

Chapter 4 provides insight into how the EU Orphan Regulation is applied in practice and defines some of the key concepts. It reflects on the implications of procedures, concepts and guidelines by providing the experiences and perspectives of different stakeholders.

Chapter 5 offers an overview of the current 'state of play' of the EU Orphan Regulation. It describes the current situation in quantitative and qualitative terms and summarises how the intervention has been implemented. Additionally, it outlines what Member States have done. An overview is included of whether there have been infringements, problems, or unintended effects. The focus herein is on aspects that are linked to the intervention. The chapter is purely descriptive in nature. A more in-depth discussion of how these findings relate to the evaluation criteria and what the implications of this are for the Regulation today and in the future is reserved for the evaluative Chapters 6 through to 10.

Chapters 6 through 10 have been structured around the different evaluation dimensions, that is: **relevance, effectiveness, efficiency, coherence and EU added value**. Within the chapters, we have followed a structure that corresponds to a significant degree with the evaluation questions contained within each of these dimensions.

Detailed discussions of the methodologies used, and of other aspects of the study, have been included as **Appendices** to this report.

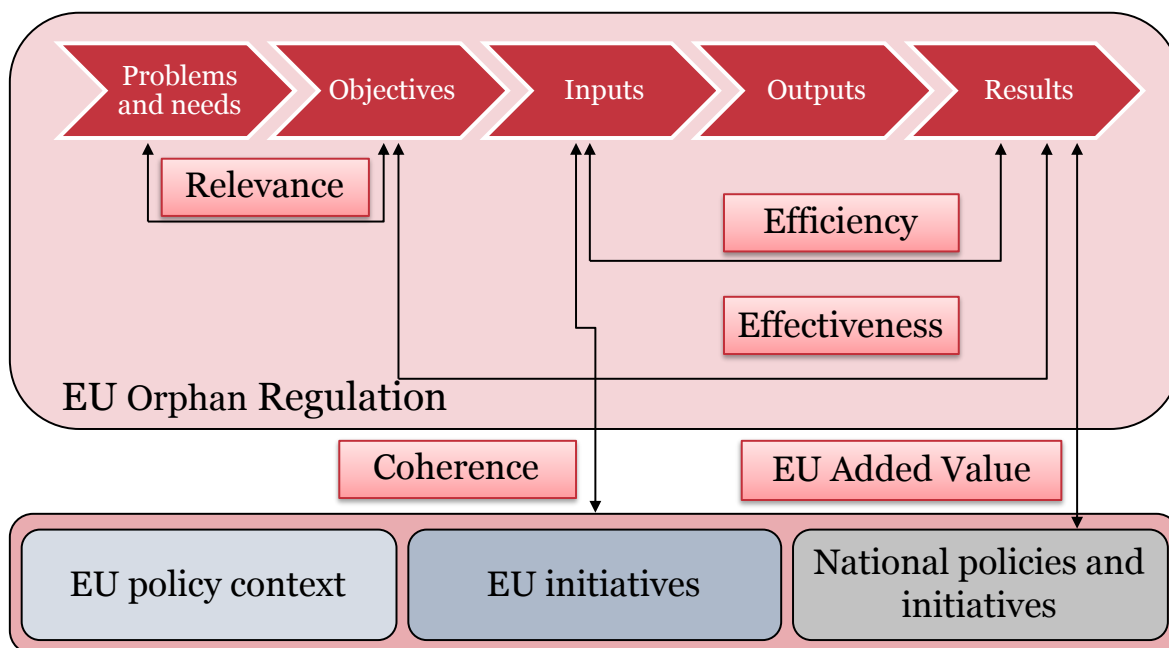
1. Background

1.1. Study objectives, evaluation questions and scope

In the Request for Services for this study, the European Commission indicated that the present study is to be seen as a first step in the process of a comprehensive joint evaluation of the EU Orphan Regulation and the EU Paediatric Regulation. This study has hereto gathered information on five evaluation criteria: A) relevance, B) effectiveness, C) efficiency, D) coherence and E) EU added value of the EU Orphan Regulation. The goal was to gather and analyse factual information on the outcomes and impacts of the Regulation, as well as to collect stakeholder perspectives on the Regulation and the implementation thereof.

Figure 2 illustrates how these evaluation criteria relate to the different steps in the intervention logic of the Regulation.

Figure 2 Definition of the evaluation criteria



The Request for Services identified 17 distinct evaluation questions, which have formed the basis for this report.

Relevance

Relevance looks at the relationship between the **needs and problems in society** and the **objectives** of the intervention and hence touches on aspects of design. (Better Regulation Toolbox #47). Specifically, the Request for Services called for an assessment of the following evaluation questions relating to relevance.

- To what extent have the specific objectives underlying the adoption of the Orphan Regulation proven to be appropriate for addressing the problems? To what extent is the current scope of application of the

Regulation catering for real (unmet) needs of patients? To what extent has, the Orphan Regulation addressed the issue of return on investment?

- To what extent are the provisions still an appropriate means for addressing one of the Regulation's main objectives, namely that patients suffering from rare diseases have access to the same quality of medicinal products as other patients within the EU? To what extent has this access been achieved across EU Member States and, if there are differences, what are the reasons for this?
- Which developments in the sector have significant implications for the Regulation's relevance and future?

Effectiveness

Effectiveness analysis considers how successful an intervention has been in **achieving or progressing towards its objectives**. It thus focuses on first determining what actions have been taken and what the outputs and results of these have been. It then traces these back to the objectives to see to what extent and in what areas they have been achieved. Factors that have contributed to or have hindered success are identified. It also considers if any unexpected or unintended effects have occurred. Specifically, the Request for Services called for an assessment of the following evaluation questions relating to relevance:

- How have the developers made use of the specific incentives provided by the Regulation and what were the reasons behind this?
- To what extent is the Orphan Regulation effective in addressing unmet medical needs?
- To what extent has the (additional) incentive for the development of 'orphan paediatric medicine' resulted in new medicinal products catering for an unmet medical need for children?
- To what extent the Orphan Regulation and its implementation contributed to the general objective of competitiveness of European pharmaceutical industry? What were factors supported or hindered attaining this objective?
- Are the provisions of the Orphan Regulation sufficiently explicit as to when market exclusivity should be granted and revoked?

Efficiency

Efficiency analysis considers the **relationship between the resources used by an intervention and the changes generated by the intervention** (which may be positive or negative). Differences in the way an intervention is approached and conducted can have a significant influence on the effects, making it interesting to consider whether other choices (e.g. as demonstrated via different Member States) achieved the same benefits at less cost (or greater benefits at the same cost). Specifically, the Request for Services called for answers to the following questions:

- Are the costs borne by the individual stakeholder reasonable in relation to the benefits (for the specific group)? Is there a fair distribution of costs between the main actors?
- Could the objectives of the Orphan Regulation have been achieved differently, i.e. at lower costs?
- How significant is the administrative burden for specific stakeholders caused by the Orphan Regulation compared to the situation before it entered into force?

Coherence

The evaluation of coherence involves looking at how well or not different actions work together. It may highlight areas where there are synergies which improve overall performance or which were perhaps not possible if introduced at national level; or it may point to tensions e.g. objectives, which are potentially contradictory, or approaches which are causing inefficiencies.

- To what extent is the Orphan Regulation coherent/complementary with other EU and national interventions in the pharmaceutical area (e.g. legal interventions for medicinal products in general, paediatrics; research programmes; national pricing mechanisms)?
- To what extent are the various tools (incentives, procedures, assistance) as set out in the Orphan Regulation work together in a coherent way?
- What are the links between the areas of orphan and paediatric medicines? To what extent, in practice, is there an overlap and how has this influenced therapeutic advances?
- To which extent is the concept of designation consistent with the marketing authorisation itself?

EU added value

EU-added value looks for changes, which it can reasonably be argued, are due to the EU intervention, over and above what could reasonably have been expected from national actions by the Member States.

- What has been the added value resulting from EU intervention in the Orphan Regulation compared to what could be achieved at international, national or regional level without such intervention?
- What is the value of non-legislative initiatives in the field of rare diseases (registries, information/epidemiological databases, etc.) for the proper functioning of the Orphan Regulation?

The time reference period for this study has been the years 2006 (where possible and applicable, data for the period 2000-2006 have been included as well) through to December 2017. All 28 EU Member States were included in the scope of analysis, where possible extended to the entire EEA area. Where possible, data was compared against information from other jurisdictions, in particular the US.

1.2. Methodology

This study has drawn from a variety of data sources. Primary data was collected from targeted stakeholder groups using a series of interviews and online administered surveys. Stakeholder groups reached through this process included representatives of:

- The European Commission: DG SANTE and DG RTD
- The European Medicines Agency (EMA)
- National representatives on the EMA Committee on Orphan Medicinal Products
- Representatives of national ministries of health or national health executive agencies
- Sponsors of orphan medicinal products and their industry associations
- Developers of generic orphan medicines and their industry associations
- Patient and consumer organisations
- Academic experts
- Regulatory agencies in the US (FDA) and Japan (PDMA)

A detailed description of the targeted consultation activities, including an overview of respondents and protocols, is included in Appendix C and Appendix D to this report.

Separately, an online public consultation was performed to solicit input from individuals with a personal experience with rare diseases (patients and carers), and from health care professionals. The public consultation has been described in more detail in Appendix E to this report.

The primary data collected was qualitatively analysed and has been included at various points throughout this report.

The primary data analysis was supported by several secondary data analysis activities. First, a comprehensive review of peer-reviewed and grey literature was conducted to contextualise findings and to address data gaps.

A thorough analysis was also performed of the portfolio of data provided by the EMA on all designated and authorised orphan medicinal products. This analysis included a number of activities by the study team to clean and categorise the available data. The detailed description of this is presented in Appendix B. Also, aggregate data on uptake and costs of incentives related to the EU Orphan Regulation were provided.

Using data provided by IQVIA and MPA Business Services¹, we have estimated the costs resulting from different elements of the EU Orphan Regulation to distinct groups of stakeholders. This analysis fed in to a quantitative cost-benefit

¹ IQVIA is a contract research and analytical services organization that collects, among others, global pharmaceutical sales data (<https://www.iqvia.com/>). MPA Business Services is a business intelligence and market research company for the pharmaceutical and health care industry providing, among others, patent analytics services (<http://mpasearch.co.uk/>). The data procured from IQVIA and MPA Business Services are described in more detail in section F1 of Appendix F.

analysis. The methodological steps taken to complete these activities have been described extensively in Appendix E and Appendix G.

1.3. Study limitations

As with any study, there are some important limitations that should be taken into account in interpretation of the here presented findings and conclusions. Specific limitations that apply to data sets have been listed in the applicable sections of the report and as part of the methodology descriptions in Appendix B and Appendix F. This section describes only the more general limitations that have bearing on the entire study.

First, whilst triangulation of information has been sought through the use of different sources of information and inclusion of a large number of stakeholders, some areas are supported by more robust information than others. Also, substantial parts of the information are inherently subjective and may depend on one's perspective. For instance, whereas representatives of patient organisations and health care payers may find certain behaviours that they observe by pharmaceutical companies ethically questionable or even unacceptable, these same behaviours are viewed by industry representatives as necessary. We have aimed to appropriately juxtapose such divergent viewpoints and, where possible, have included the relevant factual information.

Second, we recognise that the number and diversity of stakeholders for this topic exceeds that which could realistically be included in the study. It can therefore not be excluded that certain perspectives have been underrepresented. Relatively low participation from stakeholders was, for instance, found from developers of generic medicines. Whilst this stakeholder group was targeted via surveys, it is conceivable that only companies that do in fact produce generic versions of orphan medicines, participated, whereas the perspective of companies that decide *not* to engage in this would have been equally valuable.

Third, sponsors of orphan medicines were found to be unwilling or unable to provide the study team with estimates of the costs of R&D for these products. This means that all information on this cost element had to be based on the basis of available literature. Moreover, limited generic entry observed after expiry of the orphan market exclusivity has meant that estimates of the value of the market exclusivity reward rely on a small, potentially not representative, sample of products.

2. The situation for orphan medicines in Europe before 2000

2.1. Introduction

To better understand the rationale for the introduction of the EU Orphan Regulation, section 2.2 describes the situation concerning rare diseases and orphan medicines in Europe before the EU Orphan Regulation was introduced in 2000². This is then followed by a broad description of the research and policy environment prior to the Regulation's development. The chapter provides a 'baseline,' the situation that held in the period before the Regulation was introduced, against which we assess the performance of the Regulation in our later chapters. Specifically, the points of comparison considered are:

- How many medicinal products for the treatment of rare diseases were available in the EU prior to 2000?
- To what extent did patients with rare diseases have access to these treatments?
- What was the state of R&D for orphan medicinal products at the time?
- What was the policy context in which the Regulation was introduced?

Chapters 3 and 4 offer a more detailed description of the EU Orphan Regulation, its specific objectives, intervention logic and design. Together these three chapters provide the necessary background information to support the Regulation's evaluation.

Importantly, at the time the EU Orphan Regulation was prepared, the European Commission (EC) did not yet have the requirement of *ex ante* impact assessments that it has today. Therefore, no such supporting document was available to inform the baseline. Rather, this chapter draws on our stakeholder consultations and desk research, in particular a review of the following documents which were prepared by the EC prior to the introduction of the EU Orphan Regulation:

- A Commission Communication on the framework for action in the field of public health, 1993³
- A Council Resolution on orphan medicines, 1995⁴

² The terms of reference for this study specified the following: "The relevant time period is the year 2006 until end of 2017. (The Commission published a Staff Working Document in 2006 on the experience acquired with the Orphan Regulation from 2000 to 2005, which should serve as a primary baseline for this study.)". At the request of the Project Steering Group, also the situation prior to 2000 was taken into account in the construction of the baseline. However, in the absence of an *ex ante* impact assessment limited quantitative information could be identified. Moreover, that which was identified could not always be directly compared to the State of Play as, in the absence of definitions, the methods for establishing the values are not equivalent.

³ A Commission Communication on the framework for action in the field of public health (Com)93/559)

⁴ A Council Resolution on orphan medicines of 20 December 1995 (95/C 350/03)

- A Programme of Community action on rare diseases within the framework for action in the field of public health, 1997⁵
- A proposal for a European Parliament and Council Regulation (EC) on orphan medicinal products, 1998⁶

We also note that at the time the Regulation was adopted, the EU consisted of only 15 Member States⁷ compared to the 28 Member States it had at the end of 2017 (the final point in time for this evaluation). As such, the information on the baseline does not take into account the situation in the 13 Member States that joined the EU after 2000⁸. This study did not look specifically at the landscape for orphan medicines in these 13 Member States prior to 2000 or to joining the EU. However, as discussed further in Section 6.2.1, many of these are countries where access to orphan medicines currently is below the EU average. It is likely that this situation was not significantly better before these countries entered the EU single market.

2.2. Availability of and access to orphan medicines in the EU before 2000

In its opening paragraph, the Explanatory Memorandum that introduced the proposal for a new Regulation (COM/98/0450 final) noted that, although “medicine and medical research have made remarkable progress in saving lives, extending life expectancy and ridding the world of diseases”, there still remain “many diseases which cannot be treated satisfactorily and for which no medication or other diagnosis, prevention or treatment is available.” It specifically singles out diseases that affect relatively few people and the medicines to treat them, known as “orphan medicinal products” (OMPs). The proposal, however, did not indicate how many such treatments were available then on the European market.

In fact, at that time, there was no unified definition of rare diseases or of orphan medicines. For example, the 1995 interim report prepared by Saphir for the Commission of the European Communities, noted that “it is generally considered that a rare disease is one that does not strike more than 650 to 1000 people per million” (Saphir Europe, 1995). Meanwhile, under the US Orphan Drug Act, a rare disease was defined as one that affects fewer than 200,000 people in the US (approx. 7 in 10,000). Both definitions vary from what was later used in the design of the EU Orphan Regulation and from those used in various other countries (also see Section 2.5). This lack of a unified definition means that establishing how many products were on the European market before 2000

⁵ A Programme of Community action on rare diseases within the framework for action in the field of public health (COM(97)225 final)

⁶ A proposal for a European Parliament and Council Regulation (EC) on orphan medicinal products, COM/98/0450 final, COD 98/0240

⁷ Belgium, France, Germany, Italy, Luxembourg, Netherlands, Denmark, Ireland, United Kingdom, Greece, Portugal, Spain, Austria, Finland and Sweden.

⁸ In order of accession, these are: Cyprus (2004), Czech Republic (2004), Estonia (2004), Hungary (2004), Latvia (2004), Lithuania (2004), Malta (2004), Poland (2004), Slovakia (2004), Slovenia (2004), Bulgaria (2007), Romania (2007), Croatia (2013).

which would now be considered eligible for designation as an orphan medicine under the EU Regulation is extremely difficult.

According to information listed by OrphaNet, before the EU Orphan Regulation came into force in 2000, there were only 15 medicinal products intended for rare diseases with a European marketing authorisation (Orphanet Report Series, 2019). Together, these products covered 6 of the 14 main therapeutic areas, based on the ATC classification system (Table 1).⁹ All three products within ATC code B were treatments for forms of haemophilia.

Table 1 ATC classification of medicines for rare diseases with an EU marketing authorisation before 2000

ATC	L-imm	B	A	G	N	V
count	5	3	3	2	1	1
%	33%	20%	20%	13%	7%	7%

L-imm = immunomodulating agents, B = blood & blood-forming organs, A = alimentary tract and metabolism, G = genito-urinary system & sex hormones, N = nervous system, V = various.

Whilst we did not have information on the approved therapeutic indications of these 15 products in 2000, just over half (8) had an indication for paediatric use in its most recent version of the summary of product characteristics. Of those that did not, 3 were for conditions that do not affect children. For the remaining 4 products, the summary of product characteristics indicates that there are no or insufficient data to demonstrate safety and efficacy in children. It should be emphasised that these products were all authorised well before the EU Paediatric Regulation, which mandates the development and approval of a paediatric investigation plan, took effect.

Using the same data set¹⁰, another article by Gianuzzi et al. analysed the number of approved *indications* for rare conditions per year by the FDA and by the EMA in the period 1983–2015 (Giannuzzi, Conte, et al., 2017). The authors note that, before the EU Orphan Regulation came into force, there were 40 indications that had been approved centrally by the EMA. They also state that six products had been classified by the agency as “orphan-like drugs”¹¹.

Such figures are helpful to estimate the availability of what would now be considered ‘orphan medicines’ in the EU. However, as these products were never assessed against the criteria used to determine eligibility for orphan designation in the EU (including demonstration of significant benefit), it cannot be conclusively stated that they would have qualified as orphan medicines had the

⁹ The Anatomical Therapeutic Chemical (ATC) Classification System is a globally recognised system for classifying pharmaceutical active substances.
https://www.whocc.no/atc/structure_and_principles/

¹⁰ Although the authors do not list which products they included in their analysis, it appears to correspond with the number of indications for the 15 aforementioned products and thus likely is based on the same data set.

¹¹ The EMA granted fee exemptions prior to entry into force of the Orphan Regulation to 6 products (https://www.ema.europa.eu/en/documents/press-release/inaugural-meeting-committee-orphan-medicinal-products_en.pdf). Of these, 4 are included also in the OrphaNet list of 15 medicinal products for rare diseases.

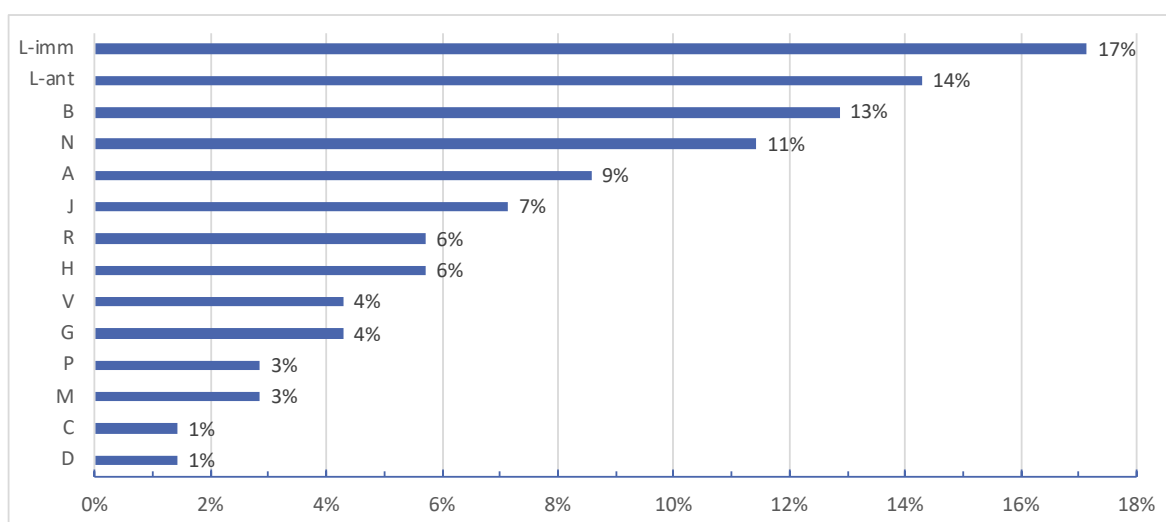
Regulation existed at the time. Therefore, they cannot be interpreted as a 'baseline' in the strict sense. Moreover, the figure also does not account for products that may have been authorised in any EU country through a procedure other than the centralised procedure, nor for products that may have been used only as a pharmacy preparation, without any marketing authorisation at all.

To further strengthen the evidence base for this benchmark number, looking not only at what products had been authorised in the EU at the time but also taking into account to what extent these were accessible to patients, we performed an analysis of products that had received a US orphan designation and that were available in the EU prior to 2000, using sales data provided by IQVIA. This comparison against these 'orphan-like' products in itself also has an important limitation: the US Orphan Drug Act uses different criteria to establish eligibility than the EU Orphan Regulation. Therefore, one cannot simply use this number as an exact benchmark. Nonetheless, the comparison gives some useful insights into the order of magnitude. (See Appendix F for an explanation how this group has been established).

This analysis indicates there were 70 orphan-like products available in at least one EU market in the period before 2000. The majority of the orphan-like products are so-called 'immunomodulating agents' (ATC codes L02-04), which are designed to affect the immune system to help the body fight cancer, infection, or other diseases (Figure 3). A related class of products (antineoplastic agents, ATC code L01) contains primarily anti-cancer medicines and forms the second largest group of products.

Figure 3 ATC classification of 'orphan-like' products on the EU market before 2000

ATC	L-imm	L-ant	B	N	A	J	H	R	G	V	M	P	D	C
count	12	10	9	8	6	5	4	4	3	3	2	2	1	1
%	17%	14%	13%	11%	9%	7%	6%	6%	4%	4%	3%	3%	1%	1%



L-imm = immunomodulating agents, L-ant = antineoplastic agents, B = blood & blood-forming organs, N = nervous system, A = alimentary tract and metabolism, J = anti-infectives, H = systemic hormonal preparations, R = respiratory system, G = genito-urinary system & sex hormones, V = various, M = musculoskeletal, P = antiparasitic, D = dermatological, C = cardiovascular.

Based on a matching of trade names, the list of 70 orphan-like products includes five of the aforementioned 15 medicinal products that were used in the estimate provided by Hernberg-Ståhl and Reljanović and by Giannuzzi et al. (Giannuzzi, Conte, et al., 2017; Hernberg-Ståhl & Reljanovic, 2013). The differences between these two data sets may be partially explained by definitional variations. **What is clear from all estimates, though, is that the number of treatments for rare diseases on the EU market was small, both in relation to the number of rare diseases and to the number of treatments for more common diseases.** It also suggests that **the number of new products coming onto the market per year was measurable in single figures.** Indeed, the proposal for the EU Orphan Regulation anticipated the number of annual orphan designations would be quite small and would build only slowly over time, from 5 in 2000 to 12 in 2003.¹²

Alongside the limited number of products being developed for rare diseases, desk research suggests that in the 1980s and 1990s, there was **also a significant delay in access to these products across EU Member States.** In a study by Rappagliosi et al., it was stated that, after patients in the first EU Member State would receive access to medication, it would typically take up to four years until all other analysed EU Member States had access as well (Rappagliosi, 2001). The authors also note that, on average, EU patients had to wait over two years after a molecule was first licensed by at least one EU Member State before it was available for use in their country. The analysis of the 70 orphan-like products shows that these products typically took 2-3 years to become available in the first EU Member State following marketing authorisation and after three years had reached 3 to 4 EU Member States.¹³

Delays in access could occur, at least in part, as a result of differences in the speed with which national authorities would process applications for marketing authorisation, in the years before the creation of the European Medicines Evaluation Agency (EMEA, renamed in 2004 to the European Medicines Agency (EMA)) and before a centralised procedure for marketing authorisation in the EU was introduced. Moreover, national procedures for reimbursement and admittance of products into the health system and some strategic launch decisions could result in delays.

2.3. Interest from pharmaceutical industry in orphan medicines development

The limited number of orphan medicines on the market in the EU before 2000 reflects the fact that, at the time, few pharmaceutical companies had products for rare diseases in their portfolio. The 15 products previously mentioned as having been authorised by the EMA before 2000, were brought to the market by 12 individual pharmaceutical companies. Beyond this, we could not determine how many companies had products with the potential to be used in treatment of rare diseases in different stages of development.

¹² See the table at the bottom of page 21 of the proposal for an EU Regulation on orphan medicinal products ((COM/98/0450 final)).

¹³ The analysis has been based on the EU12, to ensure a common comparison basis for orphan-likes introduced in 1990-1995 and those introduced after 1995.

There were some specialised institutes and companies active in the field, such as Orphan Europe, which was founded in Paris in 1999 as an independent pharmaceutical company specialising in orphan medicines (Orphan Europe, 2019). However, **for the most part the traditional 'Big Pharma' companies had ignored this space.** This was considered problematic as, according to the 1995 Saphir report, "without participation of the private Pharmaceutical industry, R&D of (new) drugs remains totally insufficient, if not impossible" (Saphir Europe, 1995).

The lack of involvement from pharmaceutical companies is widely understood to trace back to the imbalance between risk and reward, with pharmaceutical companies the world over having been unable to make a business case for investing in the development of innovative medicines for rare diseases. Each of the Commission policy documents noted there was an evident market failure around rare diseases, with pharmaceutical companies reluctant to invest in the development of innovative medicines where the small numbers of patients that might be expected to benefit from those treatments would be insufficient to recover the substantial cost to develop the product.

This imbalance in risk and reward was also part of the rationale for the introduction of the US Orphan Drug Act, and its choice of support measures that were explicitly targeted at companies' research and development activities. The pharmaceutical market was dominated by big companies, who were mainly interested in the development of 'blockbuster' medications that could be mass-marketed and sold in large volumes. There was little interest in developing medication for rare diseases (Mariz, 2015), which occur so infrequently that the high cost of developing the necessary medicinal products was unlikely to be recovered by the sale of the product in the small numbers and normal prices envisaged (European Parliament, 2000).

2.4. Environment for R&D on rare diseases

Alongside the lack of interest from the pharmaceutical industry where there is no clear commercial incentive, stakeholders have also highlighted that **even in the research community there was limited focus on rare diseases.** This meant that for the vast majority of rare diseases there was limited to no understanding of the natural history of the condition (that is: knowledge from knowing the underlying causes of a disease to how a disease progresses over time and what the impact of that is on morbidity and mortality). Without such information, product developers would be challenged to find suitable drug candidates to test and develop.

In the EU there were several programmes that aimed to improve the knowledge on rare diseases prior to the introduction of the EU Orphan Regulation. For example, the 4th EU Framework Programme for Research and Technological Development (1994-1998) contained a small amount of funding for research on rare diseases under the Biomedical and Health Research Programme (Biomed-2). This programme allocated €7.5 million in EC funding (2.5% of the €320m Biomed-2 programme) to 23 funded projects. These projects included support for basic research, clinical research, the setting up of European registries and databases and Pan-EU rare disease networks. Funding was also allocated to support for the development of a European diagnostic

quality assurance programme. A review of the programme found that it had played an important role in funding research on rare diseases, had helped launch new collaborations with the pharmaceutical industry and had been instrumental in establishing diagnostic facilities and protocols as well as biobanks and networks.

We could not identify any published reports or information on the overall volume of rare disease research that was being funded by the pharmaceutical industry or individual EU Member States in the period before the Orphan Regulation was introduced.¹⁴ Here too, the absence of an agreed definition of rare or orphan diseases plays a role. Nonetheless, the 1995 Saphir report provides some illustrative examples of research funding and activities in several Member States (Saphir Europe, 1995). In France, it notes the work of the French National Institute of Health and Medical Research (INSERM) in providing training, information and advocacy for R&D on rare diseases. In the UK, the work of the Medical Research Council and some industries is noted. Also the Nordic Council had proposed the development of a programme to collect information on rare diseases in Scandinavia, whilst in Denmark a research centre and a dedicated diagnosis and treatment facility had been founded with a focus on rare diseases.

2.5. Policy development and actions on rare diseases in the EU and at Member State level

In the 1980s, a public debate took place in the United States about rare diseases and the lack of innovation for patients with these diseases. This debate resulted in the **US Congress passing the Orphan Drug Act in 1983** (97th Congress, 1983), providing manufacturers with three primary incentives designed to encourage the availability of orphan medicines: federal funding of clinical trials; tax relief on the costs of clinical testing; and a 7-year period of market exclusivity. **The developments in the US prompted policy discussions about public health in many other countries around the world.** Japan revised its pharmaceutical legislation in 1993 with the addition of special provisions relating to R&D for orphan medicines (Orphanet, 2018b) and Australia followed with the implementation of its orphan medicine policy in 1997 (Orphanet, 2018a).

A similar debate occurred in Europe in the 1990s. Around this time, various Member States of the EU had already adopted, or had begun to adopt, specific measures to increase their knowledge of rare diseases and to improve detection, diagnosis, prevention or treatment for rare diseases, as discussed in Section 2.4 (Wilsdon et al., 2017). Additionally, some Member States had started to introduce policies referring to orphan medicines (Saphir Europe, 1995). For instance, in 1992 France introduced a provision for the exceptional use of certain

¹⁴ A Communication from the Commission on the Single Market in Pharmaceuticals (COM(1998) 588) provides some statistics on the overall size and health of the sector in the EU15 and comments on the loss of competitiveness against the US and notes the weaker performance of Europe's biotech sector in particular. It says nothing about products or research on rare diseases but does note the Commission's proposal for the Orphan Regulation. In 1997, the pharmaceutical industry invested around €10.5 billion in R&D for all areas, against an annual income of around €62 billion (R&D intensity = 17%). The same report also shows that the EU15 industry overall had around 12% of its income related to in-patent products. In principle, the in-patent products include the most innovative products. COM(1998) 588 Final, Brussels, 25 November 1998.

medicines under a set of conditions, including for the treatment of patients affected by rare diseases when there is no suitable substitute. This was followed in 1994 by a more specific instruction on how the products were to be provided (Gozlan, 1995). France also confirmed its intention to set up a procedure for 'exceptional drugs', noting the lack of clinical information on 'orphan indications'. Italy's National Health Plan for 1998-2000 introduced an initiative on rare diseases, which included a fee waiver for patients with these conditions (Congiu, 2014). Special regulatory measures for products for the treatment of rare diseases or for products with limited commercial potential but of great medical value had also been introduced in Spain and Sweden (Saphir Europe, 1995).

At a Community level, Commission Directive 91/507/EEC reduced the data requirements for marketing authorisation in exceptional circumstances and cited rare diseases as possible examples where that may be necessary, along with appropriate safeguards (e.g. a programme of studies, possible supervision by a qualified person, a notice informing practitioners about the limitations of the evidence base) (The European Commission, 1991). Additionally, the fees collected by the European Medicines Evaluation Agency, which was founded in 1995¹⁵, could be waived where commercial potential was limited.

France played an especially important role in putting rare diseases and orphan medicines high on the European political agenda. At the request of the Ministry of Social Affairs and Health, in 1994 INSERM published a review of the situation and put forward proposals for improving the situation nationally and at a European level. This report, "Les orphelins de la santé" was the beginning of a reflection on the merits of creating EU legislation to provide incentives for the development of orphan medicines (Wolf, 1994). It noted that the definition of a rare disease was set using prevalence thresholds that differed markedly from one country to another. In France for example, the threshold was one person in 2,000, whereas in Denmark and Sweden it was 1 in 10,000 and in the UK it was 1 in 50,000. It was estimated there were likely to be somewhere between 5,000 and 7,000 pathologies at the threshold level of 1 in 2,000, and that these diseases affected an estimated 3 million people in France and 25 to 30 million across Europe. The study also noted that, while these diseases affect relatively few people, they are often serious, disabling conditions and are an important source of childhood mortality.

The INSERM report provided a foundation for France to use its 1995 EU presidency to call on its 14 EU partners to establish a common policy on orphan medicines, including an agreed definition of rare diseases and funding for R&D. France argued there was a "real public health need" for an EU policy to boost R&D for orphan medicines, and that common action would allow Europe to "mobilise significant financial resources" (Lewis, 1995). According to INSERM, France also stated that EU action would allow the European pharmaceutical industry to catch up with the United States and Japan, where initiatives to stimulate development of orphan medicines had been introduced in 1983 and 1993 respectively.

¹⁵ EC Regulation 2309/93

The apparent success of the US Orphan Drug Act had stimulated interest at a European level. In the 13 years following the introduction of the Orphan Drugs Act, 837 medicinal products were awarded the status of orphan drug in the US, of which 323 had benefited from the federal grants programme (R&D support). At the end of 1997, 152 orphan products had gone on to obtain marketing authorisation and were being used by over 7 million US patients ((The European Commission, 1998a), page 2). The US programme had already benefited Europe, as evidenced by the presence of 'orphan-like' products approved for sale within the European Economic Area (EEA). However, the number of new products remained small in comparison with the extent of the estimated problem (the thousands of rare diseases without a treatment and the millions of EU citizens affected) and access to such products was uneven.

2.6. A proposal for an EU Orphan Regulation

Prior to 2000, there was insufficient knowledge of rare diseases and their impact. Likewise, there was limited detailed information on the (lack of) activity of businesses in this space. This situation prompted the Commission to call for several EU-wide initiatives – through the rare disease research area within the Fourth EU RTD Framework Programme – to improve the data available.

In late 1995, the Commission set up an expert group to discuss priorities for EU level research and regulatory action regarding rare diseases and orphan medicines (Wilsdon et al., 2017). This resulted in rare conditions being classified as one of eight priority areas in public health that could benefit from Community initiatives to complement the efforts of Member States and maximise the exchange of information and experience in the context of the Framework for action in the field of public health (1997).¹⁶

In a 1995 Council Resolution on orphan medicines, **the Council of the European Union called upon the European Commission "to look into the situation of 'orphan' drugs in Europe and, if necessary, make appropriate proposals with a view to improving access to medicinal products intended particularly for people suffering from rare diseases"** (The Council of the European Union, 1995, p3-4). The resolution called on the Commission to consider five areas, including a definition of a rare disease in terms of its prevalence and measures using regulatory provisions to promote research, authorisation and distribution of orphan medicines.¹⁷

Following consultation with Member States, industry and patient organisations, the Commission subsequently developed a proposal ((COM/98/0450 final)) for an EU Regulation on orphan medicinal products (The European Commission, 1998a). This proposal set out the baseline situation as it was understood at the time. The Explanatory Memorandum introducing the proposal, stated that (page 2):

¹⁶ See paragraph 68, page 20 of a Commission communication on the framework for action in the field of public health (Com)93/559)

¹⁷ See page 3 and 4 of the Council Resolution of 20 December 1995 on orphan drugs (95/C 350/03). This resolution is recorded in the Information and Notices of the Official Journal of the European Union, C350, Volume 38, 30 December 1995

- There was a “whole series of diseases that affect relatively few people”, and that “approximately 5,000 such diseases had been identified” for which no medication or other diagnosis, prevention or treatment is available.
- The pharmaceutical industry is reluctant to develop medicinal products to treat these diseases: “pharmaceutical research and development are so expensive nowadays that there is practically no chance of any company making the effort to develop a medicinal product, to obtain authorisation for its use and to place it on the market if it is to be supplied at normal prices to the few patients who require it. That is why such medicinal products are known as ‘orphan medicinal products’.”
- “Society cannot accept that certain individuals be denied the benefits of medical progress simply because the affliction from which they suffer affects only a small number of people. It is therefore up to the public authorities to provide the necessary incentives and to adapt their administrative procedures so as to make it as easy as possible to provide these patients with medicinal products that are as safe and effective as any other medicinal product and meet the same quality standards.”

As pointed out in the Council Resolution of 20 December 1995 on orphan medicinal products (The Council of the European Union, 1995, p.3-4), “a common European approach to rare diseases and orphan medicinal products holds advantages in epidemiological, public health and economic terms.” Given the economies of scope, a concerted European approach was judged more likely to improve matters as compared with individual national initiatives. The proposal left open, however, the possibility for Member States to provide national or local support actions, such as additional R&D incentives.

The proposed legislation was an EU Regulation, which had the benefit of not needing to be transposed into national legislation – as with a directive – and meant that the legislation would be applicable in all Member States as soon as it would enter into force, overriding national law. It allowed for the implementation of a designation procedure by the EMEA. The proposal also recommended the creation of a new committee operating within the agency, comprising persons appointed by Member States and selected based on their experience in the field of rare diseases. This newly formed Committee for Orphan Medicinal Products (COMP) benefited from the support of an EMEA provided secretariat, as well as representatives of patients’ associations.

The proposal defined harmonised criteria for defining a rare disease and introduced a Community procedure for designating orphan medicinal products, within the context of the completion of the internal market. It laid down the specific criteria, procedures and rewards. Given the complexity involved in the development of a typical orphan medicinal product, the regulatory proposal foresaw a need to allow sponsors to request assistance with the preparation of a protocol, for example, in carrying out or following up clinical trials. The proposal also foresaw access to the Community market via the centralised authorisation procedure. There was also an annual contribution from the Community budget allocated specifically to allow applicants to be exempt from paying all or part of the fees associated with the services provided. It was

assumed the fee might constitute a serious obstacle in its own right to the development of at least some orphan drugs.

The EU Orphan Regulation (EC) No 141/2000 was officially adopted by the European Parliament on 16 December 1999. A further implementing Regulation (EC) No 847/2000 was adopted by the European Commission the following year, as will be discussed further in Chapter 3.

2.7. Concluding remarks on the baseline assessment

Prior to 2000, the landscape for medicines for the treatment of rare diseases in Europe was characterised by low levels of R&D activity and a large unmet medical need. In the absence of agreed definitions of what constitutes a rare disease or an orphan medicine and an overall lack of data, an exact measure of the number of products available at that time cannot be provided. Estimates suggest the number to be in the range of around 15 to 70 products. Regardless of the exact number, the problems were clear and a need for action was felt globally.

The pharmaceutical industry had shown little interest in the absence of a clear commercial proposition for these products. The lack of activity was also observed more broadly in the research community, where rare diseases had not been a major focus. In recognition of this problem, the US introduced its Orphan Drug Act in 1983. By the late 1990s, this move was starting to have a visible impact with 152 newly authorised orphan medicines.

Following this lead, across Europe there were increasing calls for similar initiatives within the EU to further accelerate these developments and stimulate development of orphan medicines in the EU as well. The development of an EU Orphan Regulation fits within this context of a call for political and societal action. The EU Orphan Regulation (EC) No 141/2000 was officially adopted in 1999. Chapter 3 provides a further description of the EU Orphan Regulation itself.

3. The EU Orphan Regulation

3.1. Introduction

In this chapter, we outline the **objectives and design of the EU Orphan Regulation**, based on a discussion of the intervention logic. This logic elaborates the connection between the identified problems and the chosen policy intervention (the Regulation), drawing out the connections between the inputs, outputs and outcomes.

The chapter also describes the principal components of the Regulation's design and its implementation. This is followed by a discussion of how the regulatory framework has evolved over time, in light of operational experience and case law, as reflected in new and additional guidelines.

The final section of this chapter compares key aspects of the EU Orphan Regulation with similar initiatives in the US, Japan and Australia.

3.2. Objectives of the EU Orphan Regulation and intervention logic

In the preceding chapter the backdrop against which the EU Orphan Regulation was crafted was presented. Here, it was demonstrated that the Regulation was intended to respond to the fact that patients with rare diseases did not have the same access to treatments as patients with other diseases, and that product development had been largely ignored by the pharmaceutical industry. Therefore, a Regulation was adopted that aimed to stimulate such development by providing a set of incentives.

The EU Orphan Regulation shares not only its overarching objectives with the US Orphan Drug Act, but also substantial parts of its design.

Similar to its older sibling, the EU Orphan Regulation offers a set of incentives aimed at (potential) developers of orphan medicines to encourage them to invest in the development of these products to a greater extent than they would do under normal market conditions. Each of these incentives will be discussed in more detail in section 3.3.5.

The most prominent of all incentives has been the so-called orphan market exclusivity: the EU Orphan Regulation grants developers of designated orphan medicines exclusive marketing rights throughout the EU single market for a 10-year period upon marketing authorisation.

The Regulation also allows Member States to introduce their own additional incentives for placing orphan medicines on the market, within the framework of their own powers and responsibilities, such as R&D tax credits.

To support this assessment of the EU Orphan Regulation, the EC has created an intervention logic which, based on the original documents supporting the development and adoption of the Regulation, reflects the intended objectives and design elements (Figure 4). This logic translates the problems with availability of and access to orphan medicines, as described in the previous chapter, into a series of discrete objectives.

Specifically, this intervention logic identifies the following objectives:

- To ensure a high level of health protection for all

- To ensure the same quality of treatment to patients with rare diseases
- To restore the equilibrium between supply (industry) and demand (patients with rare diseases)
- To provide incentives for industry to develop and market orphan medicinal products
- To ensure better functioning of the internal market and preserve fair competition
- To encourage innovation

It is worth emphasising that **not all of these objectives are entirely within the competences of the EC.**¹⁸ As will be discussed in more detail in various parts of this report, access to treatment depends also on national health policies, as health care is a national responsibility of the Member States. Therefore, whilst these objectives should be seen as part of the overarching goals to which the Regulation intends to contribute, the extent to which they are achievable is limited by actions at the level of the national policy context.

Additionally, the objectives of promoting the functioning of the internal market and encouraging innovation are not at the heart of the EU Orphan Regulation itself. Rather, these have been derived from the broader policy context in which the EU Orphan Regulation was introduced (see hereto also Section 2.5).

The objectives are being addressed through *inputs* coordinated by the EMA and the Commission. These inputs include the criteria and processes for orphan designation, and the centralised authorisation procedure for orphan medicinal products (OMPs)¹⁹. By linking these to a set of incentives the Regulation is expected to deliver an increase in business expenditure on R&D for orphan medicines and ultimately contribute to an increase in the number of successfully developed orphan medicines (*results*). Additionally, the aim is to improve the financial and political environment to support rare disease research and the development of orphan medicines.

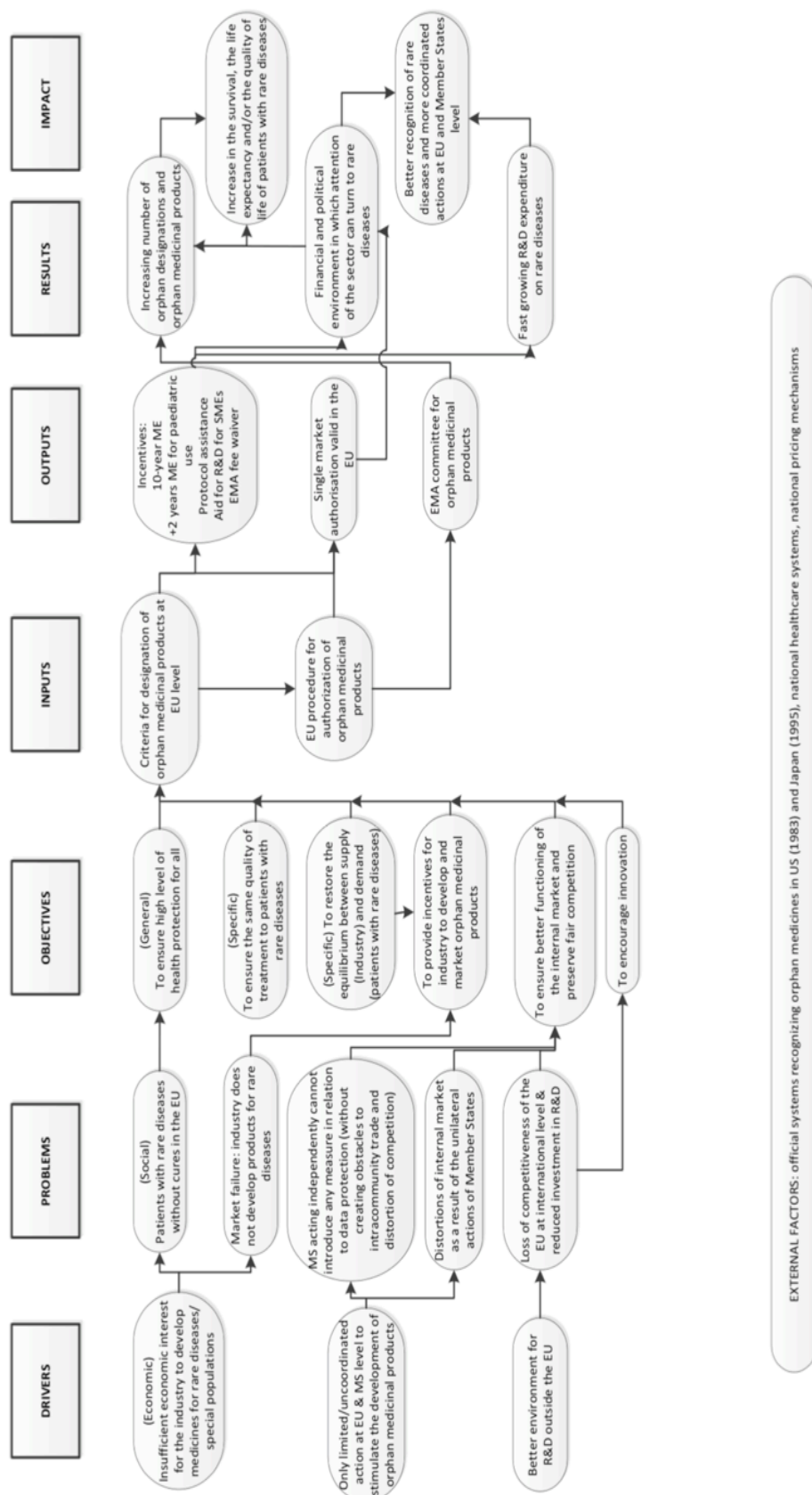
An increase in the numbers of authorised orphan medicines is expected to be concomitant with increased availability of treatments for rare diseases across the EU. In the longer-term, improved availability of and access to orphan medicines is expected to deliver improvements in the quality of life for the European citizens living with those conditions (*impacts*).

The next section of this chapter describes the various elements of the Regulation, taking into account their link to the objectives and to observable results and impacts.

¹⁸ Under Article 168 of the Treaty of Lisbon, public health is a shared competence between the EU and Member States. This competence is limited to the aspects defined in the Treaty on the Functioning of the European Union and excludes national health policy and health services delivery. https://eur-lex.europa.eu/summary/glossary/public_health.html

¹⁹ Throughout this report the term orphan medicine has been used for products that have been authorized in the EU with maintenance of orphan designation.

Figure 4 Intervention logic for the study to support the evaluation of the EU Orphan Regulation



3.3. Design of the Regulation

To evaluate the performance of the Regulation, it is important to understand its basic design and operational arrangements.

3.3.1. Designation criteria

The criteria for orphan designation are first introduced in Article 3 of Regulation 141/2000. It states that a product is eligible for designation if a sponsor can establish:

- 1a) that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition **affecting not more than five in 10 thousand persons** in the Community when the application is made, or
- 1b) that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community and that without incentives it is **unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment.**

and

- 2) That there exists **no satisfactory method** of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of **significant benefit** to those affected by that condition.

The Implementing Regulation 847/2000, as well as additional guidelines provide further clarification on the interpretation of these criteria. This is discussed on more detail in Section 3.4.

The proposal for the Regulation notes that in the US initially an economic criterion was used to determine eligibility for orphan designation, wherein it “had to be established that the costs of developing the medicinal product and supplying it to the general public could not reasonably be expected to be covered by sales of the medicinal product in the United States.”(The European Commission, 1998b) However, this was amended a year later by adding a concurrent epidemiological criterion.

The proposal acknowledges that use of an epidemiological criterion could offer incentives to products that subsequently prove “to be (extremely) profitable” but counters this with the claim that, in the US, this happened only in “approximately 1% of all designations!”.

Nevertheless, the proposal included a provision that “where it can be established that the marketing of an orphan medicinal product is proving more profitable than had been foreseen, any Member State may request that the exclusive marketing rights be withdrawn at the end of the sixth year following issue of the authorisation”. To this end, Article 8(2) of the draft proposal was formulated as follows: “This [market exclusivity] period may however be reduced to six years if, at the end of the fifth year, a Member State can establish that the criteria laid down in Article 3 are no longer met in respect of the medicinal product concerned or that the price charged for the medicinal product concerned is such that it allows the earning of an unreasonable profit”. In the final text of the

Regulation, however, the wording of this provision had been subtly changed to state that the market exclusivity period may be reduced only if “it is established, in respect of the medicinal product concerned, that the criteria laid down in Article 3 are no longer met, *inter alia*, where it is shown on the basis of available evidence that the product is sufficiently profitable not to justify the maintenance of market exclusivity.” The consequence of this change is that, where in the draft proposal, the market exclusivity could be reduced on either of two independent grounds, the final wording of the Regulation only permits this on the grounds at which the designation was granted. In other words, if orphan designation was granted on the basis of fulfilment of the prevalence criterion, the market exclusivity cannot be reduced on the basis of profitability.

3.3.2. Committee for orphan medicinal products

Article 4 of Regulation 141/2000 dictates the creation of a ‘Committee for Orphan Medicinal Products’ (COMP) with the following tasks:

- To examine any application for the designation of a medicinal product as an orphan medicinal product which is submitted to it in accordance with this Regulation
- To advise the Commission on the establishment and development of a policy on orphan medicinal products for the European Union
- To assist the Commission in liaising internationally on matters relating to orphan medicinal products, and in liaising with patient support groups
- To assist the Commission in drawing up detailed guidelines.

It furthermore specifies that the COMP shall comprise of:

- a chair, elected by serving COMP members
- one member nominated by each of the Member States (currently 28)
- three members nominated by the European Commission on the Agency's recommendation
- three members representing patients' organisations nominated by the European Commission
- Representatives of the Commission and the Executive Director of the Agency or his representative may attend all meetings of the Committee.

At present, the COMP also contains members nominated by Iceland and Norway. COMP members are appointed for a renewable term of three years. The composition and tasks of the COMP are laid down in its Rules of Procedure.²⁰

3.3.3. Procedures for designation and removal

The procedures for designation and removal from the register of orphan medicinal products are laid down in Article 5 of Regulation 141/2000. The respective roles of the EMA and European Commission in these procedures are discussed in the next chapter.

²⁰ https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/committee-orphan-medicinal-products-rules-procedure_en.pdf

Parties seeking to apply for an orphan designation can either submit their application directly or can request a pre-submission meeting to informally discuss the draft application and obtain feedback from the coordinators on likely weaknesses in the application.²¹ Hereto, one week before these meetings, a draft application should be submitted.

Once submitted, **the applications are reviewed by the COMP**. The COMP can decide to invite the applicant to provide an oral explanation at a COMP plenary meeting. It should adopt an opinion within 90 days. When a negative opinion is deemed inevitable, the applicant is given the opportunity to withdraw the application. The applicant also has the option to appeal a negative opinion. After the COMP has adopted its opinion, the EC has a further 30 days from receipt to issue a decision.

3.3.4. Centralised authorisation procedure

Article 7 of Regulation 141/2000 gives sponsors access to the centralised authorisation procedure which grants the marketing authorisation holder the right to bring a product to market in all EU countries at the same time²². Whilst initially, access to this procedure was optional, with the adoption of Regulation (EC) No 726/2004 **the centralised authorisation procedure became mandatory for all designated orphan medicines**.

3.3.5. Incentives

The Regulation introduced a comprehensive set of tools to incentivise developers of medicinal products at various points throughout the R&D pathway, from early stages of research through to the point of placing a product on the market. These comprise:

- **Market exclusivity** (article 8 of the EU Orphan Regulation), which creates for the marketing authorisation holder an additional temporary exclusivity right (in addition to the regular protection of medicinal products)
- **Protocol assistance** (article 6 of the EU Orphan Regulation), which offers the sponsor of a designated orphan medicine the possibility to request advice from the EMA on the conduct of tests and trials necessary to demonstrate the quality, safety and efficacy of the medicinal product
- **Fee waivers** (article 7 sub 2 of the EU Orphan Regulation), which offers total or partial exemptions from the payment of fees for applications for designated orphan medicines. Typical fees for marketing authorisation applications are from €291,000 and annual fees are around €104,600.²³
- **Aid for research** (article 9 of the EU Orphan Regulation), which makes it possible to create other incentives to stimulate the development and

²¹ <https://www.ema.europa.eu/en/human-regulatory/research-development/orphan-designation/applying-orphan-designation>

²² It does, however, not grant the marketing authorisation holder access to national reimbursement systems.

²³ <https://www.ema.europa.eu/en/human-regulatory/overview/fees-payable-european-medicines-agency#fees-for-marketing-authorisations-section>, last accessed July 2019.

marketing of orphan medicines, at the level of the EU or individual Member States

The following sections further describe each of these incentives.

Market exclusivity

The development of pharmaceutical products asks for significant *ex ante* R&D investments. These investment decisions are influenced by the expected ability to recoup these investments later on. The patent system was designed to allow inventors a time to recover their investments and make a fair profit, by protecting their market from competitors for a limited amount of time. In return, once the product is no longer under protection from a patent (or other form of intellectual property right), other companies are allowed to create copies of the product. **This system of intellectual property rights of time-limited market protection in exchange for sharing knowledge, is intended to create a pharmaceutical market in which both innovators and generic manufacturers can thrive.** The premise is that patients can benefit from potentially life-saving new treatments whilst having access to competitively priced generic versions of existing treatments.

However, in the preparation of the EU Orphan Regulation, it was recognised that **the existing intellectual property rights system was insufficient to stimulate the development and marketing of orphan medicines and that additional incentives were needed.** Hereto, a 10-year period of market exclusivity was introduced, in line with a similar incentive in the US (Article 8 of the EU Orphan Regulation).

This exclusivity means that **a regulatory competent authority cannot authorise the same or a 'similar' medicine for the same orphan indication, nor can it take an application for authorisation into consideration whilst an exclusivity period is in effect on a first product,** even when that product is not protected by a patent.²⁴ The fact that the EMA cannot even consider an application for a similar product whilst there is still an active market exclusivity means that in practice the effective period of protection from market exclusivity can exceed the 10-year period.

The 10-year period was chosen to match the period of regulatory protection (data exclusivity and market protection) as it was at the time of inception (which was 10 years in 2000, currently 11 years (8+2+1) for centrally authorised products). It can be extended by two more years if the application for a marketing authorisation includes the results of all studies conducted in

²⁴ Article 8 of Regulation 141/2000 states: 'Where a marketing authorisation in respect of an orphan medicinal product is granted (...) or where all the Member States have granted marketing authorisations in accordance with the procedures for mutual recognition (...) the Community and the Member States shall not, for a period of 10 years, accept another application for a marketing authorisation, or grant a marketing authorisation or accept an application to extend an existing marketing authorisation, for the same therapeutic indication, in respect of a similar medicinal product.' A marketing authorisation for a product similar to one under market exclusivity can only be granted if one of the derogation options under Article 8(3) of Regulation (EC) No 141/2000 applies.

compliance with an agreed Paediatric Investigation Plan (PIP).²⁵ Market exclusivity for orphan medicines is cumulative with patents/supplementary protection certificates and with existing regulatory frameworks for data exclusivity and market protection.²⁶ Although the scope of market exclusivity differs somewhat from that of data exclusivity and market protection, the general market implications are similar: delay of generic entry in the market.²⁷

In addition to specifying when a product may receive the orphan market exclusivity, Article 8 also contains clauses that detail when the exclusivity period may be reduced (sub 2) or when a derogation to the exclusivity can be granted (sub 3).

Article 8.2 states that the market exclusivity period may be reduced to six years if:

- “at the end of the fifth year, it is established, in respect of the medicinal product concerned, that the criteria laid down in Article 3 are no longer met, *inter alia*, where it is shown on the basis of available evidence that the product is sufficiently profitable not to justify maintenance of market exclusivity. To that end, a Member State shall inform the Agency that the criterion on the basis of which market exclusivity was granted may not be met (...) The sponsor shall provide the Agency with the information necessary for that purpose.”

Article 8.3 details that “a marketing authorisation may be granted, for the same therapeutic indication, to a similar medicinal product if:

- the holder of the marketing authorisation for the original orphan medicinal product has given his consent to the second applicant, or

²⁵ See article 37 of Regulation No 1901/2006 on the Regulation on medicinal products for paediatric use.

²⁶ **Data exclusivity** is a form of protection conferred on the dossier of trial results that the marketing authorisation holder submitted to obtain approval. The exclusivity means that for a period of 8 years, a company that seeks to produce a generic version of the product cannot reference the data. The scope of protection thus differs from the market exclusivity in that the protection is on the *data* rather than on the *product*.

After the 8-year data exclusivity, the marketing authorisation holder still is entitled to a 2-year period of **market protection** during which it has the sole right to market the product. One additional year of market protection (represented by '+1') can be granted in the case of:

1. Additional therapeutic indications with significant therapeutic value,
2. New indications for well-established substances, or
3. When new data is submitted to support a change in classification.

During the period in between the expiry of data exclusivity and that of market protection, third parties can file for a marketing authorisation by referring to the data of the reference product but cannot yet bring the product on the market. This differs from the orphan market exclusivity, during which the EMA will not yet consider any such applications. Together, the scope of protection from data exclusivity and market protection also differs from that of market exclusivity in that all subsequent variations of the product or any additional indications *cannot* trigger a new period of protection, as these would come under the same *Global Marketing Authorisation*.

²⁷ The difference in protection also results in a difference in market entry barriers for generic drug developers: orphan market exclusivity may result in a longer delay of generic entry.

- the holder of the marketing authorisation for the original orphan medicinal product is unable to supply sufficient quantities of the medicinal product, or
- the second applicant can establish in the application that the second medicinal product, although similar to the orphan medicinal product already authorised, is safer, more effective or otherwise clinically superior”

Protocol assistance

While the market exclusivity reward can be seen as the major incentive for the development and marketing of orphan medicines (European Commission, 2008), particularly for the eventual marketing authorisation holder, **the EU Orphan Regulation also foresees in the provision of a specific form of scientific advice by the EMA, known as ‘protocol assistance’** for orphan medicine developers (Article 6) (European Medicines Agency, 2018).²⁸ This implies that, in addition to the general scientific advice EMA can provide on appropriate tests and studies in the development of a medicine, orphan medicine developers can seek advice in relation to the criteria for authorisation of orphan medicines.

The tenet behind the introduction of protocol assistance appears to be that **the Regulation relies on certain unique concepts, such as significant benefit**. Therefore, orphan medicine developers, in particular those with limited or no prior experience in this space, could benefit from having a good and early understanding of the Regulation’s requirements for eligibility and how these apply to their products.

Developers of orphan medicines can request protocol assistance before marketing authorisation and, as of July 2015 when the EMA initiated a 12-month pilot, also for post-authorisation safety studies.

Fee waivers

If sponsors obtain a marketing authorisation or make use of other services of the EMA, they normally have to pay certain fees (European Medicines Agency, 2017c). Various main fee categories can herein be distinguished, including:

- Centralised procedure, covering fees for the application, extension and variations to a marketing authorisation
- Scientific advice
- Scientific services (Article 7 sub 2)

The system contains various exemptions, such as fee reductions for small or medium-sized enterprises (SMEs), some fee reductions in case of multiple applications on usage patent grounds, as well as fee reductions for designated orphan medicines. The latter is funded by a special annual contribution to the EMA (Article 7 sub 2).

²⁸ Article 6 of Regulation 141/2000 states: “The sponsor of an orphan medicine may, prior to the submission of an application for marketing authorisation, request advice from the Agency on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of the medicinal product (...)”.

In the introduction to Regulation 141/2000 it is explained that patients with rare conditions “deserve the same quality, safety and efficacy in medicinal products as other patients; orphan medicinal products should therefore be submitted to the normal evaluation process; sponsors of orphan medicinal products should have the possibility of obtaining a Community authorisation; in **order to facilitate the granting or the maintenance of a Community authorisation, fees to be paid to the Agency should be waived at least in part.**”²⁹

Aid for research

Besides the market exclusivity reward, the protocol assistance and the fee waiver, the EU Orphan Regulation introduced the incentive ‘aid for research’ (Article 9).³⁰ This incentive makes it **possible for the European Commission and/or Member States to provide additional funding for the research and development of designated products.** The self-evident intent of this incentive is to further encourage investments in, in particular, the early stages of research into rare diseases. Such basic research is important to elucidate the mechanisms underpinning rare diseases, which in turn is a prerequisite for product development.

3.4. Evolution of the EU Orphan Regulation

Regulation 141/2000 laid down the Community procedure for the designation of orphan medicines, for providing R&D incentives and for placing on the market of designated orphan medicines. As such, it forms the basic framework for what is referred to as the ‘EU Orphan Regulation’. However, the original Regulation identified several follow-up actions needed to effectively implement the Regulation. Specifically, it stated:

- In consultation with the Member States, the Agency and interested parties, the Commission shall draw up detailed guidelines on the form in which applications for transfer shall be made and the content of such applications and all the particulars of the new sponsor. (Article 5.11)
- The Agency shall draw up a procedure on the development of orphan medicinal products, covering regulatory assistance for the definition of the content of the application for authorisation within the meaning of Article 6 of Regulation (EEC) No 2309/93. (Article 6.2)
- The Commission shall adopt definitions of ‘similar medicinal product’ and ‘clinical superiority’ in the form of an implementing Regulation. Those measures, designed to amend non-essential elements of this Regulation

²⁹ Article 7 sub 2 of Regulation 141/2000 states: “A special contribution from the Community (...) shall be allocated every year to the Agency. The contribution shall be used exclusively by the Agency to waive, in part or in total, all the fees payable under Community rules adopted pursuant to Regulation (EEC) No 2309/93.”

³⁰ Article 9 of Regulation 141/2000 states: ‘Medicinal products designated as orphan medicines under the provisions of this Regulation shall be eligible for incentives made available by the Community and by the Member States to support research into, and the development and availability of, orphan medicines and in particular aid for research for small- and medium-sized undertakings provided for in framework programmes for research and technological development.’

by supplementing it, shall be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 10a(3). (Article 8(4))

- The Commission shall draw up detailed guidelines for the application of this Article in consultation with the Member States, the Agency and interested parties. (Article 8(5))

In response to these identified follow-up actions, the **Implementing Regulation No 847/2000**, laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and the definitions of the concepts 'similar medicinal product' and 'clinical superiority' was adopted in April 2000 (Commission of the European Communities, 2000b).

Since then, the **EU Orphan Regulation has undergone several, relatively minor evolutions**, the majority of which are **clarifications** as to the exact meaning of the terminology and procedures defined in the original Regulation. These have mostly been formulated based on the experiences of operating the Regulation. There are also several changes that relate to developments in science and technology that have necessitated further guidance.

In addition, there have been wider policy developments that have had implications for the EU Orphan Regulation. The **2006 Paediatric Regulation** is a case in point, which created the **possibility for orphan paediatric medicines to be granted two additional years of market exclusivity**³¹. Other examples originate outside the realm of public health, such as EU enlargement and support for SMEs.

The following provides a selection of some key developments, cross-referencing the amendment or additional guidance to the original Regulation:

- **Criteria for designation.** On 29 July 2003, the Commission issued communication 2003/C 178/02, providing further clarification on the interpretation and application of the Regulation, specifically Articles 3 (criteria for designation), 5 (procedure for designation and removal from the register), and 7 (Community marketing authorisation). This communication was replaced by the 2016 **Commission Notice 2016/C 424/03**.
- **Centralised authorisation procedure.** On 31 March 2004, the European Parliament and Council adopted **Regulation (EC) No 726/2004**, which determined that all marketing authorisations for orphan medicines in the EU should follow a centralised authorisation procedure. Previously, the centralised procedure had been optional but it remained possible also to use national procedures. However, following a review by the Commission, it was decided to mandate a central procedure in all cases. This was prompted in part by various technological advances, which were making the assessment process more demanding scientifically, and by the increased likelihood of differential approaches following EU enlargement.

³¹ Section 29 of Regulation (EC) No 1901/2006.

- **Fee reductions and exemptions for SMEs.** On 15 December 2005, the European Commission adopted **Regulation (EC) No 2049/2005** regarding the payment of fees to, and receipt of assistance from, the EMA by SMEs. It applied to all SMEs and all medicines; and was prompted by a concern to reduce the barriers to medicines innovation faced by small technology businesses. It determines that scientific advice and scientific services for designated orphan medicines shall be provided by the EMA to SMEs free of charge
- **Conditional marketing authorisations.** On 29 March 2006, the European Commission adopted **Regulation (EC) No 507/2006**, which provides the legal framework for the granting of a conditional marketing authorisation to medicines that fall within the scope of Regulation (EC) No 726/2004 (e.g. public health emergencies). It establishes that orphan medicines are one such category where the data limitations are highly likely and where an opinion can be based on less complete data (with a positive risk-benefit balance). A conditional marketing authorisation would allow medicines to come in to use earlier and with the assumption that missing data may be gathered in time such that a (unconditional) marketing authorisation might be issued
- **Extension of market exclusivity for orphan paediatric drugs.** On 12 December 2006, the European Parliament and Council adopted **Regulation (EC) No 1901/2006** on medicinal products for paediatric use. It establishes that the usual period of market exclusivity for orphan medicines may be extended from 10 to 12 years (+2 years) if study results are submitted in compliance with an agreed paediatric investigation plan (PIP) at the time of marketing authorisation
- **Clarification of the COMP procedure** followed in any early review of the period of market exclusivity. On 23 September 2008, the Commission published **Guideline 2008/C 242/07** on aspects of the application of Article 8(2) of Regulation (EC) No 141/2000: review of the period of market exclusivity of orphan medicinal products.
- On 18 November 2016, the Commission adopted **Commission notice 2016/C 424/03** on the application of Articles 3 (criteria for designation), 5 (procedure for designation and removal from the register) and 7 (Union marketing authorisation) of Regulation (EC) No 141/2000 on orphan medicinal products. This notice sets out the Commission's interpretation on certain matters relating to the implementation of the designation and the market exclusivity provisions. These included clarifications around the prevalence calculations for products intended for prevention (e.g. vaccines). The guideline also included new advice about the eligibility of products that would be applicable to communicable diseases (e.g. Ebola, Zika) that are widespread outside Europe and constitute a serious threat to public health in Europe even though the prevalence threshold would not apply.
- **Commission Regulation (EU) 2018/781** amending Regulation (EC) No 847/2000, which outlines the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal

product and provides definitions of the concepts "similar medicinal product" and "clinical superiority".

The interpretation of the Regulation is further shaped by the outcomes of legal challenges. Whilst a full analysis of all jurisprudence involving the interpretation of the EU Orphan Regulation was not performed for this study, a representative for the EC indicated that the EC had been a party in approximately eight cases wherein pharmaceutical companies challenged decisions by the EC or EMA. These were said to mostly refer to Articles 3 and 5 of the Regulation and to the granting of the market exclusivity.

Notable cases involving the EMA/EC include:

- Teva v the European Medicines Agency (Case T-140/12) involving the product Glivec (imatinib). This case is discussed in more detail in section 9.1.2
- Case T-452/14 Laboratoires CTRS v European Commission, involving the products Orphacol and Kolbam. The case centred on how to interpret the concept of similarity for products with different therapeutic indications under the same orphan indication. The court ruled that it was not sufficiently demonstrated that Kolbam was clinically superior to Orphacol, which was still under market exclusivity. The marketing authorisation for Kolbam was consequently annulled, even after overlapping indications were removed from the Summary of Product Characteristics as the summary still contained information referring to the overlapping indications. This case demonstrated that bringing a similar product to market can be done only if one of the three exceptions of Art. 8(3) is met and there is absolutely no overlap possible between the two marketing authorisations, not even in any of the documentation that is part of the dossier. (de Jongh, Radauer, Bostyn, & Poort, 2018)
- Bristol-Myers Squibb Pharma EEIG v European Commission and European Medicines Agency, involving the products Empliciti (elotuzumab) and Kyprolis (Carfilzomib). The case centred on the ability to demonstrate significant benefit over products that were approved only after an application was filed with the European Medicines Agency for the newer product. The ruling confirmed that significant benefit needs to be demonstrated over all available alternative treatments, even if those alternative treatments had not yet been authorised at the time clinical trials were conducted for the product for which the new marketing authorisation is sought.

The effect of such cases and rulings is to **create precedent for future interpretations**. In each of the above cases, the rulings confirmed the interpretation of the Regulation by the EMA

Court decisions are binding and cannot be overruled by guidelines. The only recourse the EC has, if it disagrees with the outcomes of court decisions is to appeal the ruling or, ultimately, to issue an amendment of the Regulation.

Consistency with other EU policies

Regulation (EC) No 141/2000 was **designed to complement several other European Community policies**, including the 1997 Commission's Communication concerning a Programme of Community action on rare diseases within the framework for action in the field of public health (The European Parliament & The Council of the European Union, 1997).

The Programme of Community Action included 4 actions:

- Creation of a European information network on rare diseases
- Training on rare diseases for professionals to improve detection, recognition, intervention and prevention in the field of rare diseases
- Transnational collaboration between groups of persons directly or indirectly affected by rare diseases to encourage continuity of work and transnational cooperation
- Support at Community level the monitoring, surveillance and early warning for clusters of rare diseases.

The Programme provided the definition of a rare disease as a disease which has a prevalence of 5 per 10,000 or less in the Community. This prevalence threshold was subsequently also used as the main criterion for orphan designation within the EU Orphan Regulation.

The regulatory proposal also recommended an extension to the work being carried out on rare diseases under the Biomedicine and Health Programme (Biomed 2) of the **Fourth EU Framework Programme for Research and Technological Development** (1994-1998)(Wilsdon et al., 2017). The Quality of Life and Living Resources thematic programme then took up the rare disease agenda of the **Fifth Framework Programme**.³²

Last, the EU Orphan Regulation – and specifically its incentives to encourage and increase industrial investment in R&D for orphan medicinal products – was designed to align with the wider policy objective of **support for innovation and a stable legislative environment for pharmaceutical research in the European Union**, as was described in 1993 in an European Commission Communication.³³

3.5. Comparison to other international policy initiatives

The EU Orphan Regulation has been modelled to a significant extent on the US Orphan Drug Act. This Act also served as the inspiration for frameworks in other jurisdictions, such as Japan. The following sections review some of the key elements of the frameworks in the US, Japan and Australia and details how these compare to the EU framework. A summary is contained in Table 2.

³² See Slide 9 of the presentation: Horizon 2020, EU Funding for Rare Disease Research, Irene Norstedt, Head of Unit, Innovative and Personalised Medicine Unit, DG Research and Innovation (Oslo, May 2017).

³³ COM 93 718 final document

Variations in the interpretation between the frameworks are discussed in more detail in Chapter 4.

3.5.1. United States of America

In the US, the **Orphan Drug Act** (ODA), which went into effect in 1983, encourages the development and marketing of medicines to treat rare diseases and conditions. The ODA incentivises this through a combination of tax credits of 50% for expenditures incurred during the clinical testing phase for orphan medicines, an exemption from fees required when filing a new drug or biologic application and a 7-year market post-approval exclusivity provision granted for orphan drug indications designated by the US Food and Drug Administration (FDA) (Hall & Carlson, 2014; Seoane-Vazquez, Rodriguez-Monguio, Szeinbach, & Visaria, 2008a).

The FDA has offered grants totalling more than US\$18 million in 2015, through the Orphan Products Grants Program, which is administered by the FDA's Office of Orphan Product Development (OOPD). The programme provides funding for clinical research in rare diseases (Connor & Cure, 2011). Eligibility for grant funding is extended to medical devices and medical foods for which there is no reasonable expectation of development without such assistance. The OOPD also provides scientific advice to developers of designated orphan medicines.

The ODA has been credited with a positive effect on the development of orphan medicines (Freeman, Burke, Imoisili, & Cote, 2010) **and the number of product approvals for rare diseases and conditions** (Seoane-Vazquez, Rodriguez-Monguio, Szeinbach, & Visaria, 2008b). In the period 1983–2015, the FDA granted 3,647 orphan drug designations and 554 marketing authorisations for medicines targeting a total of 277 individual rare diseases (Rodriguez-Monguio, Spargo, & Seoane-Vazquez, 2017).

Although the orphan medicines developed since the introduction of the ODA have included lifesaving medicines for children, development of medicines for exclusively paediatric orphan diseases has happened to a lesser extent (Connor & Cure, 2011). In 1997, the FDA Modernization Act provided manufacturers six months of additional market exclusivity as incentive for conducting paediatric studies (U.S. Congress, 1997). The **Best Pharmaceutical Practices for Children Act** (BPCA; 2002, 2007) extended the exclusivity provisions and included a number of modifications to address the paediatric information gap. Subsequently, the **Paediatric Research Equity Act** (PREA; 2003, 2007) made sure that the FDA could ask for paediatric studies for drugs and biologics. Both programmes have helped bridge the paediatric drug development gap substantially.

The **US Creating Hope Act** offers a limited number of transferable vouchers for accelerated drug review by the FDA for developing a successful medicine for a rare paediatric disease (Rose, 2017). Such vouchers can be sold to pharmaceutical competitors for up to several hundred million dollars. However, a 2016 FDA report showed the FDA's preference for a more regulatory approach with more power to mandate paediatric studies for new biologics (US Food and Drug Administration, 2016) which would be comparable to powers the EMA and the Paediatric Committee have already had for the past decade or so.

On 18 August 2017, the **RACE (Research to Accelerate Cures and Equity) for Children Act** was signed into law as Title V of the 2017 FDA Reauthorization Act to amend PREA (US Congress, 2017). This act targets R&D towards discovering new treatments for children with cancer, an aspect that was not covered by the PREA previously. According to this Act, which will come into force in 2020, paediatric investigation may be required for medicinal products intended for adults and directed at a molecular target that the FDA determines to be “substantially relevant to the growth or progression of a paediatric cancer.” In addition, this act amends the PREA exemption for orphan-designated indications.

3.5.2. Japan

The Japanese government **introduced support for research and development of orphan drugs in 1985**. Support consists of both administrative incentives, such as a fast-track marketing authorisation procedure and consultation and advice to companies launching orphan drugs, and financial incentives, such as funds to cover a proportion of the expenditure devoted to research and development of orphan drugs, reimbursement of up to 50% of the development costs, and a 6% tax reduction for R&D expenses. Companies making profits on sales of orphan medicines must return a proportion of the subsidy granted as a contribution to these funds (Orphanet, 2018b).

The Ministry of Health, Labour and Welfare provides a free consultation service specifically for orphan drug designation applicants. (Sharma, Jacob, Tandon, & Kumar, 2010) Additional incentives include access to a fast-track approval process, which generally proceeds much smoother than that of regular medicines. Also, for orphan medicines product renewal is every 10 years, compared to every 6 years for other medicines.

3.5.3. Australia

The Australian **Orphan Drugs Policy was set up in 1997**. This orphan drug programme allows the Australian Therapeutic Goods Administration (TGA) to use information from the US *Food and Drug Administration* Orphan Drugs Programme as part of the Australian evaluation process. Additional criteria are also established for identifying and evaluating orphan medicines in Australia, which have not been evaluated in the US or do not meet the US criteria. Research and development of orphan medicines is not supported by grants or tax incentives, although the TGA covers all the costs of the orphan designation process, and then balances its expenditures with other components of the health care system overall budget (Orphanet, 2018a).

3.5.4. Summary of incentives for orphan medicines in different jurisdictions

As the preceding sections show, different jurisdictions have developed substantially different frameworks for stimulating the development of orphan medicines (Table 2). The US and EU are, by comparison to Japan and Australia, the most-wide ranging in terms of the range of incentives offered. Australia has the most limited framework.

As will be discussed in more detail in Sections 4.4 and 5.2.1, these and other differences between the frameworks contribute to considerable variations between the numbers of orphan designations and authorised orphan medicines in the respective jurisdictions. These differences complicate any direct comparison to assess their relative effectiveness.

Table 2 Comparison of incentives offered by the EU, US, Japanese and Australian regulatory frameworks to support orphan medicine development

	EU	USA	Japan	Australia
Year of introduction	2000	1983	1985	1997
Financial incentives	Fee reductions / waivers	Tax credits, fee waivers	Subsidies for research, fee waivers, tax credits and reductions	Fee waivers
Market exclusivity	10 (+2) years	7 years	None	No
Scientific advice (protocol assistance)	Yes (free)	Yes (free)	Yes (reduced fees)	No
Aid for research	EC Framework Programmes	FDA Orphan Products Grant Program; NIH grants	Grants programmes	No
Regulatory tools to accelerate approval	Priority medicines (PRIME); centralised procedure; conditional approval; approval under exceptional circumstances; accelerated assessment	Fast-track approval; Breakthrough designation; Accelerated approval pathway; Priority review designation	Priority review; Fast-track approval	No

Source: (Mariz et al., 2016).

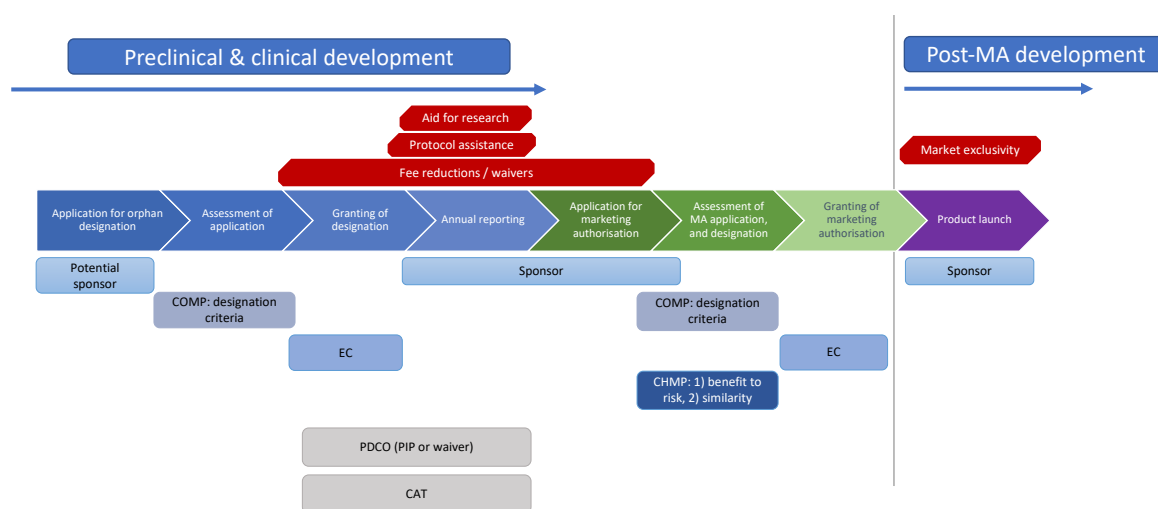
4. Application of the EU Orphan Regulation

4.1. Introduction

Chapter 3 provided an overview of the objectives and design of the EU Orphan Regulation, including how it has evolved over time. This chapter further explains how the regulatory framework is then put into practice. It introduces the various actors that are involved in the application processes (Section 4.1), discusses the key concepts that need to be understood (Section 4.2), how eligibility for orphan designation is assessed (Section 4.3), reviews how the outcomes of application of the EU Orphan Regulation compare to those in other jurisdictions (Section 4.4) and looks into the relationship between the orphan designation and the marketing authorisation of orphan medicines (Section 4.5).

Figure 5 summarises the main processes and actors involved from the initial application for designation to the moment a product is authorised and launched. It does not review the processes involved in reimbursement and launch decision-making, however, which happen at the national level.

Figure 5 Overview of steps from application for designation to product launch



COMP = Committee for Orphan Medicinal Products; PDCO = Paediatric Committee; PIP = Paediatric Investigation Plan; CAT = Committee for Advanced Therapies; CHMP = Committee for Medicinal Products for Human Use; MA = Marketing authorisation.

4.2. Roles and responsibilities of involved actors

4.2.1. European Commission

As described in Chapter 3, the EU Orphan Regulation was developed in response to a 1995 Council Resolution from the Member States. The subsequent drafting of the Regulation was then tasked to the European Commission, Directorate General for Health and Food Safety (DG SANCO, now DG SANTE). Before its implementation, Regulation No 141/2000 was formally adopted by the European Parliament and Council.

The EC currently holds various responsibilities in connection to the Regulation. The first involves the process of **granting or confirming an orphan designation** (Article 5). Whereas the assessment is done by the European Medicines Agency, the agency herein effectively acts on behalf of the EC (Article 5.4). Any decisions on eligibility for designation still need to be formally approved by the EC, via DG SANTE (Article 5 sub 8). To this end, the EMA (via the COMP) will send a report outlining its scientific opinion on all applications to DG SANTE, which will review the opinions.

The formal decision to grant a designation or not, or to maintain it at the time of marketing authorisation, is thus made by the EC. A representative of the EC may attend all meetings of the EMA Committee for Orphan Medicinal Products (Article 4 sub 5). Whilst it is possible for the EC and EMA to disagree, the two bodies aim for alignment and, should the EC have any concerns or questions about the assessment conducted by the EMA, it would normally raise these at an earlier stage than at the designation approval stage. The EC maintains an online overview of all active designations, the **Community Register on Orphan Medicinal Products**.³⁴

Second, in addition to officially granting and confirming orphan designations, the EC maintains an important role in shaping the interpretation and implementation of the Regulation, as it is responsible for the **preparation of Guidelines, Commission Notices and Implementing Regulations** that are part of the regulatory framework (Article 3 sub 2, Article 5 sub 3). Although the formal responsibility rests with the EC, staff members of the EC and EMA have indicated that the preparation of such texts is normally a joint task of the two bodies.

As already discussed in the previous chapter, a third role played by the EC, according to EC representatives, is **as a party in litigation** brought by a company (or other party) against the EC or the EMA **at the Court of Justice of the European Union**. In case litigation is brought against the EMA, the EC would exercise its right to intervene.

The division of roles and responsibilities between the EC and EMA in relation to the EU Orphan Regulation differs to a degree from that for the Paediatric Regulation. Under the Paediatric Regulation, the EMA has somewhat more authority to independently make decisions, such as on the approval of submitted Paediatric Investigation Plans (PIPs). Under the EU Orphan Regulation, by contrast, the **role of the EMA is essentially restricted to conducting the scientific assessment and reporting its findings to the EC**. In interviews, both parties have indicated that the difference is mostly historic in origin, as in 2000 the EMA was not as developed as it was in 2007 when the Paediatric Regulation was introduced. Also, according to the EC, there has been an evolution in the understanding of which type of decision-making power can be given to Agencies.

In addition to the aforementioned responsibilities, the **EC also plays an essential part in internal coordination of activities** relating to, for instance, research for rare diseases and the EU legal framework for pharmaceutical

³⁴ http://ec.europa.eu/health/documents/community-register/html/reg_od_act.htm?sort=n

products, **as well as in communication** about the Regulation, its implementation and related issues.

4.2.2. European Medicines Agency

The EMA is the executive agency responsible for the operational implementation of the EU Orphan Regulation. Alongside the regular tasks the agency conducts for all medicinal products for human and veterinary use regarding the process of scientific assessment for marketing authorisation, it is also **responsible for the correct application of the EU regulatory framework for orphan medicines** (i.e. the EU Orphan Regulation, as well as all applicable Guidelines, Commission Notices and Implementing Regulations).

The EMA provides the secretariat for the COMP. It hereto has a dedicated 'orphan team'. This team supports COMP in its assessments and in the preparations of opinions and coordinates the applicable processes within the agency. Depending on the type of product (e.g. advanced therapies), the type of sponsor (e.g. small and medium-sized enterprises), or the type of condition or indication (e.g. necessitating paediatric investigation), different EMA Committees may also be involved. The following sections introduce the main committees that may be involved throughout the development of an orphan medicine, from the moment of first application for designation until the marketing authorisation.³⁵ These descriptions are non-exhaustive and focus mainly on aspects that intersect with the application of the EU Orphan Regulation.

Committee for Orphan Medicinal Products (COMP)

As already discussed in the preceding chapter, the implementation of the Regulation depends greatly on the activities of the COMP. **The COMP meets every month to discuss applications to assess their eligibility against all applicable criteria (e.g. prevalence, medical plausibility, significant benefit), determine the orphan indication, adopt opinions and prepare summary reports**, which are then sent to the EC. These meetings currently take around three days each time.

Whereas it is at the discretion of the Member States to decide who they would like to nominate, the COMP internally seeks for a good balance of expertise by having members who represent different clinical fields and backgrounds. Many hold positions in national ministries or national competent authorities, whereas others hold positions in academia or clinical practice. However, all members are nominated on a personal title.

During the monthly COMP meetings, the committee will hold closed-door discussions. Applicants and sponsors seeking maintenance of their designation at marketing authorisation may be invited to parts of the meeting to provide oral explanations. The COMP may also invite experts, including representatives of eligible patients and consumer organisations, to attend part of the meeting when it requires expertise that is not, or not sufficiently, available among the COMP members.

³⁵ As the procedures for pharmacovigilance are not different for orphan medicines than for non-orphan products, the Pharmacovigilance Risk Assessment Committee (PRAC) is not included here.

Committee for Medicinal Products for Human Use (CHMP)

All products for which a marketing authorisation is sought through the centralised procedure must be assessed by the Committee for Medicinal Products for Human Use (CHMP), regardless of whether they have an orphan designation. **The CHMP will conduct a scientific assessment to establish the benefit to risk ratio of the product**, and thus determine whether the product should be allowed onto the European market and, if so, for which therapeutic indication(s).

The purpose of the scientific assessment performed by the CHMP is thus a different one from that conducted by the COMP, which focuses on the fulfilment of the criteria for orphan designation. Chapter 9 offers a more detailed discussion of the interactions between the CHMP and the COMP from the perspective of various stakeholders.

The CHMP is also responsible for assessing similarity for applications for marketing authorisation for products with an orphan designation in case there is already an authorised product on the market for the same orphan indication that is still protected by market exclusivity (see also section 4.5.2).

Paediatric Committee (PDCO)

Since the introduction of the Paediatric Regulation in 2007, developers should submit a 'Paediatric Investigation Plan (PIP) for all products "not later than upon completion of the human pharmacokinetic studies"³⁶. (The European Commission, 2001)).

Only when there is sufficient justification that paediatric investigations are not warranted, such as when the product targets a condition that does not affect children, can the obligation to submit a PIP be waived. In case of compliance with an agreed PIP, a marketing authorisation holder is eligible for the so-called 'paediatric extension', a 6-month extension of the Supplementary Protection Certificate (SPC) (see also Section 9.1.2). In the case of designated orphan medicines, however, a different reward is offered in the form of an additional two years of orphan market exclusivity (see also Section 3.2).

All PIPs are assessed by the Paediatric Committee (PDCO), including in the case of designated orphan medicines. The Paediatric Regulation and the Orphan Regulation intersect at the point where products are being developed for the treatment of rare diseases that occur in children. In such cases, both the COMP and the PDCO have roles to play in the regulatory assessment process. The interaction between the two committees and the processes involved is discussed further in Section 9.1.2.

Committee for Advanced Therapies (CAT)

As discussed in more detail in Section 6.3.1., an increasing share of orphan medicines fall into the category of 'advanced therapy medicinal products' (ATMPs). **In 2007, the new EU Regulation for ATMPs, Regulation (EC) No 1394/2007, was introduced** (The European Parliament and Council, 2007)

³⁶ Section 5.2.3 of Part 1 of Annex 1 of Directive 2001/83/EC)

which “lays down specific rules concerning the authorisation, supervision and pharmacovigilance of advanced therapy medicinal products” (Article 1).

Along with the introduction of the Regulation, the Committee for Advanced Therapies (CAT) was established, which is responsible for assessing the quality, safety and efficacy of advanced therapy medicinal products (ATMPs). The interaction between the CAT and COMP, as well as between the processes involving orphan designated ATMPs is discussed further in Section 9.1.

The EMA offers a range of advisory services and incentives to support the development of ATMPs, including fee reductions and scientific advice.³⁷ These incentives are all linked to EMA services and procedures. Unlike in the case of the Orphan Regulation and the Paediatric Regulation, the ATMP Regulation does not provide any incentives in the form of extended market exclusivity rights. The incentives conferred by the ATMP classification are cumulative to those that come with the orphan designation.

4.2.3. EU Member States

As highlighted previously, the EU Member States were a driving force behind the design and adoption of the EU Orphan Regulation. They maintain a degree of involvement with the regulatory framework for orphan medicines, as **the development of Guidelines and Commission Notices usually includes a process of dialogue with and consultation of the Member States** through, among others, discussion in Commission expert committees. However, Member States need not formally ratify these and have no formal right to oppose.

As discussed previously in Section 3.3.3 there is one important aspect of the Regulation for which Member States have sole responsibility, namely in relation to **invoking the reassessment procedure offered by Article 8(2) of the Regulation**. This article allows the period of market exclusivity to be reduced to six years if, after five years on the market, the orphan criteria are no longer met (European Parliament, 2000). If a Member State is of the opinion that there is reasonable doubt that the criteria are still met, it can request a reassessment by the COMP. Any request needs to be triggered by at least one EU member state. The **evidentiary burden to support the request falls on the requesting Member State(s)**, as the sponsors are under no obligation to routinely submit data. This procedure is discussed in more depth in Section 7.6.

4.3. Eligibility for orphan designation

As discussed in Section 3.3.1, Article 3(1) of the EU Orphan Regulation stipulates that a designation can be granted either on the basis of prevalence (no more than 5 in 10,000) or on an economic criterion (insufficient return on investment). In case an alternative treatment for the targeted condition already exists, the product for which designation is sought also needs to show significant benefit.

To determine whether a product is eligible, the COMP relies on a set of definitions and directions provided in the Regulation and further refined in

³⁷ <https://www.ema.europa.eu/en/human-regulatory/research-development/advanced-therapies/support-advanced-therapy-developers>

subsequent Guidelines and Commission Notices. This has been discussed in more detail in chapter 3.3.1. The following sections discuss the key aspects of the considerations the COMP must make to recommend (or not) orphan designation.

4.3.1. Defining an orphan condition

As there is no globally agreed definition of what constitutes a 'rare condition', the frameworks in the US, Japan and EU each use their own definitions to determine what is in scope. Under the EU Orphan Regulation, the term 'orphan condition' refers to a condition that has a prevalence of no more than 5 in 10,000 people, based on epidemiological data for the European Economic Area. The Orphanet Consortium maintains the Orphanet rare disease nomenclature (Orphanet, n.d.). Using this European definition, Orphanet estimates that, to date, six to seven thousand rare diseases have been discovered and new ones continue to be identified.

However, as interviews with EMA representatives and COMP members make clear, **the definition of what constitutes an eligible condition rests not only on disease prevalence, but also on the very definition of a 'condition' itself.** The EU Orphan Regulation has defined a condition as "**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).**" (The European Commission, 2007) This explicitly excludes different degrees of severity or disease stages. Also, subsets of patients where a positive benefit-risk ratio is expected are generally not considered sufficient to define a distinct condition, although the issue of sub-setting populations based on biomarkers has been under some discussion. A further discussion of this issue is presented in Section 6.3.4.

Unlike the EMA, the FDA permits a degree of sub-setting such that a medicine intended for use in a valid *orphan subset* of the population can be eligible for orphan designation even if that disease is not rare. Such sub-setting is allowed when "use of the drug in a subset of persons with a non-rare disease or condition may be appropriate but use of the drug outside of that subset (in the remaining persons with the non-rare disease or condition) would be inappropriate owing to some property(ies) of the drug." ("Electronic Code of Federal Regulations, Title 21, 316A General Provisions," 2018) Paediatric subpopulations, for instance, can constitute a valid orphan subset of a non-rare disease or condition (U.S Food and Drug Administration Center of Drug Evaluation and Research, 2018). Despite this greater flexibility, interviewed representatives of the FDA have indicated that such sub-setting is rare.

The applicant is required to provide details of the condition, based on published references. When applicable, the application should refer to the condition according to accepted international disease classification systems, such as the World Health Organisation's International Classification of Disease. (The European Commission, 2007) Although the targeted condition will normally be proposed by the sponsor seeking an orphan designation, **it is at the discretion of the COMP to determine whether it accepts this proposal as appropriate or, if not, issue an opinion for an alternative designation of the condition it considers suitable.** In the designation, the COMP deliberately

defines a condition as broadly as possible since often the designation decision needs to be made well before the therapeutic indication of the product can be established and the therapeutic indication must fall within the scope of the designated orphan indication.

4.3.2. Relation between orphan condition, therapeutic indication and product

Under both the EU and US frameworks, **the orphan designation is granted to the combination of an active substance and a particular use of the product.** This use is what is referred to as the '**orphan indication**'. It specifies if the medicinal product which is the subject of the orphan designation is intended for diagnosis, prevention or treatment of the aforementioned orphan condition. This orphan indication, however, is a distinct concept from that of the **therapeutic indication**. In the EU, orphan indications are purposely defined as broadly as possible.

The therapeutic indication, on the other hand, is dependent on the demonstrated benefit-to-risk profile of the product in certain groups of patients affected by the orphan condition. The product would be authorised only for use in the therapeutic indication(s) and this information is what is contained within the Summary of Product Characteristics (SmPC). The therapeutic indication will therefore normally be (much) narrower in scope than the orphan indication (Box 1).

For instance, the product *Translarna* has an orphan designation for the treatment of Duchenne muscular dystrophy. This combination of an application (treatment) and a condition (Duchenne muscular dystrophy) represents the orphan indication. However, according to the therapeutic indication, the product is only authorised for use "in ambulatory patients aged 2 years and older".³⁸ This means the product is not approved for use in Duchenne patients for whom the disease has advanced to the point that they can no longer walk or in very young children.

The potentially confusing distinction between an orphan indication and a therapeutic indication becomes particularly important in the context of discussions around so-called 'indication stacking'. This occurs when a single product obtains more than one orphan designation. Multiple such orphan designations could trigger multiple periods of market exclusivity. However, it should be emphasised that **any new therapeutic indication that is added to the marketing authorisation, but that falls within the scope of the designated orphan indication does not trigger a new period of market exclusivity.** Only if a product is designated and subsequently authorised for more than one *orphan indication*, each referring to distinct orphan conditions, can subsequent designations trigger a new market exclusivity period. These periods may run in parallel, with their own start and finish dates.

Because in both the EU and US the orphan designation is conferred to the active substance rather than the medicinal product, **any change to the product formulation or route of administration falls within the scope of the**

³⁸ https://www.ema.europa.eu/en/documents/product-information/translarna-epar-product-information_en.pdf

existing orphan designation (Hall & Carlson, 2014; Messina & Deneux, 2016)(Commission of the European Communities, 2016a). Only when a new product formulation can be plausibly argued to provide significant benefit, can an orphan designation for a new formulation be considered.

Box 1 Practical application of the concepts of orphan condition, orphan indication and therapeutic indication

- **Orphan 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) that meets the criteria defined in Article 3 of Regulation (EC) No 141/2000;
- **Orphan indication:** the proposed indication for the purpose of orphan designation. This specifies if the medicinal product which is the subject of the designation application is intended for diagnosis, prevention or treatment of the orphan condition.
- **Therapeutic indication:** at the time of the orphan designation application, the sponsor proposes a therapeutic indication. The therapeutic indication granted at the time of marketing authorisation will be the result of the assessment of the quality, safety and efficacy data submitted with the marketing application and may be different from that initially proposed. The therapeutic indication can also be changed or expanded after marketing authorisation on the basis of new clinical evidence.

4.3.3. Assessment of disease prevalence

The most challenging part of the application and assessment procedures is usually obtaining reliable prevalence data for the EU as a whole (Hall & Carlson, 2014). It is necessary to provide a properly referenced analysis of prevalence based on published literature.³⁹ If the prevalence rate is close to the cut-off of 5 per 10,000, some sensitivity analyses may be needed to convincingly show that the prevalence of the disease is really within the range for rare diseases according to the EU definition.

The initial burden of proof for establishing that a condition has a prevalence of no more than 5 in 10,000 is with the sponsor applying for orphan designation. The COMP will validate the sponsor's estimate. It will also confirm if the sponsor's calculations are consistent with prior calculations for the same orphan condition, where possible. In cases where the COMP questions a sponsor's calculations, or when the disease prevalence is approaching the eligibility threshold, it may ask companies to provide additional evidence such as sensitivity analyses. Problematically, however, for many diseases there are

³⁹ https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/points-consider-calculation-reporting-prevalence-condition-orphan-designation_en.pdf

no reliable data and no useful patient or disease registries (for more on registries, see also section 5.9).

Prevalence as such is much less frequently, and also less reliably, reported in the epidemiological literature (the determination of incidence, i.e. the rate of new cases of a disease, is inherently/methodologically much less demanding compared to determination of full point prevalence, the number of patients with a disease at a particular point in time). Therefore, **reported prevalence values in the literature may not have the precision required to unequivocally determine a condition to affect less than 5 in 10,000**. This lack of precision is especially difficult to accommodate for diseases close to the threshold and for which there is uncertainty or even doubt that it fulfils the designation criteria.

The lack of comprehensive reporting affects both the sponsors seeking orphan designation – particularly for conditions that have not previously been designated – and the COMP, as the latter will be challenged to validate the estimates provided.

In addition to a shortage of reliable data sources for establishing prevalence, **the calculation of prevalence itself can be challenging**. This is particularly true in the case of diseases where patients can experience periods of relapse and remission, such as many forms of cancer. **Prevalence reflects the relationship between incidence⁴⁰ and the average duration of a condition**. The consequence of using prevalence as the relevant index is the inclusion of diseases with a comparatively high incidence but a high fatality rate (and therefore short average disease duration) into the orphan disease framework. An interesting point is that **the duration of a condition cannot be equated to the duration of product use**. Although it certainly has an economic impact whether a product is used life-long or continuously (maintenance treatment), repeatedly (for relapsing/remitting diseases) or once (e.g. modified grafts for stem cell transplantation), the frequency of use of a product is not considered in the eligibility for orphan designation.

In view of the importance of the duration of a condition, the definition of when – and how long – a patient is considered affected by a condition is specifically difficult for heterogeneous conditions. Heterogeneity of conditions is, however, very common. The heterogeneity of conditions may be further increased by the requirement that different stages or severities of a “distinct medical entity” should not be regarded separately for the purpose of designation (The European Commission, 2007).

The question then is whether to count prevalence based on only those patients who have ever had a diagnosis or as the multiplication of all patients in one year (incidence) and mean disease duration. An alternative approach to the latter method is to consider **partial prevalence**, which has been defined as prevalence calculated from the number of persons whose diagnosis was made within a given period of time. (Colonna et al., 2015)

⁴⁰ Incidence reflects the rate at which new cases of disease are being added to a population through diagnosis. Prevalence represents the proportion of a population that has a condition at a specific time. It is influenced by both the rate at which new cases are occurring and the average duration of the disease.

A **2016 Commission Notice** provides **further guidance on how the calculation of prevalence should be performed** in the case of products intended for the diagnosis or prevention of a condition, or in the case of a condition outside of the European Union. (Commission of the European Communities, 2016a) In the first case, the Notice clarifies that *“the prevalence calculation of those persons affected by the condition should be based on the population to which such a product is expected to be administered on an annual basis.”* The second case potentially applies to serious communicable diseases, such as Ebola or Zika virus, that do not normally occur within the EU but for which there may be a substantial affected population outside of the EU. Here, the Notice clarifies that a low prevalence or prevalence of approximately zero in the EU renders a product potentially eligible for designation, provided that all other criteria are also met.

In contrast to the EU, the US and Japan use criteria that are not based on relative prevalence but on the absolute numbers of patients in these countries. In the US, a rare disease is one that affects fewer than 200,000 people (approx. 7 in 10,000). (Mariz et al., 2016)

Japan requires that the estimated number of patients does not exceed 50,000 (approx. 4 in 10,000). Alternatively, a disease can be designated as “Nanbyo”, according to the Japanese Pharmaceuticals and Medical Devices Agency (PDMA). The term Nanbyo, literally meaning ‘difficult illness’ is used in Japan to refer to rare and undiagnosed diseases.(Adachi et al., 2017) As of September 2018, a total of 331 diseases have been designated as Nanbyo. Diseases designated as Nanbyo are rare diseases, and its numbers of patients are regularly counted under this designation system. Patients with a designated Nanbyo disease can receive financial support for medical treatment.

4.3.4. Demonstrating insufficient return on investment

It is generally believed that **lack of product development for rare diseases is significantly related to expectations of low return on investment on these products**. It is therefore unsurprising that the EU Orphan Regulation explicitly enables a sponsor to seek designation when it can plausibly argue that without incentives it would be *“unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment”*. It could in fact be argued that ‘expectation of insufficient return’ represents the real *raison d’être* of the Regulation, whereas **prevalence could be seen more as a proxy measure by linking the former to the limited size of the market**.

However, **situations are conceivable also where there is limited commercial potential even though the prevalence exceeds the prevalence threshold value**. Article 2B of the 2016 Commission Notice confirms that such products are eligible for designation but indicates that eligibility *“will be assessed on the basis of all past and future development costs and expected revenues”*(Commission of the European Communities, 2016b).

The FDA similarly provides the possibility of granting orphan designation to products that *“will not be profitable within 7 years following approval by the FDA”*. FDA representatives have indicated that in the US too this possibility is very rarely used, but no explanation was provided for this observation.

4.3.5. Demonstrating medical plausibility and significant benefit

Whilst disease prevalence is an important assessment criterion, fulfilment of this requirement is insufficient for a product to be eligible for an orphan designation under the EU Orphan Regulation. **Additional criteria apply that relate not to the targeted condition, but rather to characteristics of the product and their relation to unmet medical need**, as discussed in this section.

A sponsor must provide sufficient data to support the rationale for the development of the product in the proposed condition, referred to as '**medical plausibility**'. This usually requires the submission of preclinical and/or preliminary clinical data. Though the submission of *in vivo* data is not a formal prerequisite, in the absence of such data, the COMP would be challenged to find significant benefit, where demonstration of this is necessary. (Mariz et al., 2016) The evidentiary standards for orphan designation differ somewhat between the EU, the US and Japan. (Messina & Deneux, 2016). In Japan, orphan designations are usually only granted to products that are in advanced clinical development (Phase II trials or further). The framework herein offers room for interpretation (Sharma et al., 2010). The US framework is more similar to that in the EU, granting designations to products in earlier stages of development where it deems there is sufficient 'scientific rationale' for the use of the medicine to support this.

For a product to be granted orphan designation it must also be demonstrated that "there is **no satisfactory treatment** for the condition in question in the EU or, if there is, the product in question will be of **significant benefit** to patients affected by that condition." **The EU Orphan Regulation thus requires a sponsor to provide details of "existing methods, which may include authorised medicinal products, medical devices or other methods of diagnosis, prevention or treatment, which are used in the Community [European Union]'**

The notion of satisfactory treatment has been further clarified in the 2016 Commission Notice (Commission of the European Communities, 2016a). This explains that any product that has been authorised in one Member State of the EU and that is for the treatment of the same disease or, at the very least, address exactly the same set of symptoms should be deemed a satisfactory method. **Only authorised products should be taken into account**, meaning that products that are used for treatment of the orphan condition 'off-label'⁴¹ are outside of the scope of comparison. Non-pharmacological methods, by contrast, could be considered as a satisfactory method. Also, **in certain cases, 'magistral formulae' and 'official formulae'**⁴², **may be considered as**

⁴¹ Off-label use refers to use of a medicine for an unapproved indication or in an unapproved age group, dosage, or route of administration. (<https://www.ema.europa.eu/en/glossary/label-use>)

⁴² Articles 3(1) of Directive 2001/83/EC defines a magistral formula as "any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient". According to Article 3 (2), official formula refers to "Any medicinal product which is prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia and is intended to be supplied directly to the patients served by the pharmacy in question." These types of products are also commonly referred to as hospital or pharmacy preparations.

satisfactory treatment if they are well known and safe and are in general practice in the EU. (The European Commission, 2001).

The intent of the latter clarification on comparison to hospital formulations has been to limit use of the Regulation in potentially undesirable ways when sponsors apply for orphan designations on products that have long been in use in the medical community and for which they have not had to substantially invest in clinical research. However, it has proven problematic to apply, as there is **often very limited information available on the use of hospital preparations in the scientific literature.** Although sponsors are expected to do due diligence and provide all available evidence from own studies and literature, the COMP has limited means at its disposal to verify whether the information is complete. COMP representatives may seek out information on the use of hospital preparations in their own countries, but this frequently entails substantial work without guarantee of success, as indicated by some COMP representatives.

When no other satisfactory treatment has been identified, and all other criteria are met, the product may be granted an orphan designation. If, however, there are alternative treatments, the EU Orphan Regulation framework requires a sponsor to demonstrate **'significant benefit'**. **A product can be said to provide significant benefit if it confers a clinically relevant advantage or offers a major contribution to patient care over existing authorized medicinal products or methods at the time of designation.**⁴³

Since, at the time of initial designation, there may be limited data available to substantiate the claim of significant benefit, **the sponsor may base its justification on certain assumptions, the validity of which will be assessed by the COMP.** In the assessment required for confirmation of orphan designation at the time of marketing authorisation, however, the sponsor will need to provide adequate data to further substantiate the claim of significant benefit. Once the designation is confirmed, the EMA and COMP have no mandate to independently reopen an assessment if new information becomes available that would call into question the eligibility. The only recourse in such a case is the option to initiate a procedure under Article 8(2) of the EU Orphan Regulation, which needs to be invoked by at least one Member State.

The term 'significant benefit' bears similarities to the concepts of 'clinical superiority' and 'high medical need' that are used in the US and Japan respectively. In the US, the concept of 'clinical superiority' is used. However, unlike in the EU, this concept is not used at the time of the initial orphan designation. Rather, when a marketing authorisation for a designated orphan product is requested, the FDA will assess whether the product is not the 'same' as one already on the market and under regulatory protection.

The 'same' herein means that a medicine either contains the same active moiety as a previously approved medicine (for small molecule medicines) or contains

⁴³ The 2016 Commission Notice clarifies that demonstration of significant benefit may be based, for example, on *'improved efficacy for the entire population suffering from the condition or a particular population subset or a subset that is resistant to the existing treatments'*, or *'significantly improved adherence to treatment due to a change in pharmaceutical form, provided there are documented difficulties with the existing formulation(s) or route of administration'*.

the same principal molecular structural features (for macromolecules) and is intended for the same use. If the medicine is found to be the 'same' it can only obtain the orphan market exclusivity if it is demonstrably 'clinically superior', meaning that it shows greater effectiveness, is safer or otherwise makes a major contribution to patient care. The Japanese system grants orphan designation to products for which there is an alternative treatment only when higher efficacy or safety is expected compared with existing products.

4.4. Comparison of Regulations between EU and other jurisdictions

Sponsors of orphan medicines often submit applications to the EMA and to the FDA in parallel (Messina & Deneux, 2016). There is a common application form for both agencies that covers administrative information. However, the scientific documentation to prove that all qualifying criteria are being met must follow local requirements and thus must be adapted according to the region in question.

Because of the discussed differences between the regulatory frameworks in the EU, US and Japan, some products may be designated as 'orphan' under one but not under another. There are important differences between the regulatory frameworks in the EU, US, Japan and Australia with regards to the definition of medical need, comparator products and even the definition of an orphan condition, resulting in differences in approvals between these jurisdictions (Table 3).

Table 3 Comparison of criteria for orphan designation in the EU, US, Japan and Australia

	EU	US	Japan	Australia
Prevalence condition	< 5 in 10,000 in EEA.	< 200,000 in US. (At a population of 325 million, this approximates a ratio of 6 in 10,000 ⁴⁴)	< 50,000 in Japan (At a population of 127 million this approximates a ratio of 4 in 10,000 ⁴⁴) Nanbyo designated condition.	< 5 in 10,000 in Australia.
Medical need	No satisfactory methods of treatment (or prevention or diagnosis) exist, OR; If any such methods exist the medicinal product must be of significant benefit to those	Clinically superior: shown to provide a significant therapeutic advantage over and above that provided by an approved drug in one or more of the following ways:	High medical need: • no appropriate alternative drug/medical device/regenerative medical product or treatment for the disease; OR • when higher efficacy or safety is	No other therapeutic goods intended to treat, prevent or diagnose the condition are included in the TGA register, OR If any such product exists, the medicine provides a significant

⁴⁴ In 2017, according to <https://data.worldbank.org/indicator/sp.pop.totl>

	EU	US	Japan	Australia
	<p>affected by the condition, i.e.:</p> <ul style="list-style-type: none"> ▪ conferring a clinically relevant advantage; or ▪ a major contribution to patient care. 	<p>(i) Greater effectiveness;</p> <p>(ii) Greater safety in a substantial portion of the target populations;</p> <p>(iii) In unusual cases, where neither greater safety nor greater effectiveness has been shown, a demonstration that the drug otherwise makes a major contribution to patient care.</p>	<p>expected compared with existing products.</p>	<p>benefit in relation to efficacy, safety or a major contribution to patient care</p>
Comparator	<p>Any medicinal product (orphan or non- orphan) holding a national or centralised EU marketing authorisation, as well as well-known and safe magistral formulations or nonpharmacological methods.</p>	<p>Only (FDA) approved medicinal products.</p>	<p>Any existing products.</p>	<p>Any therapeutic goods included in the TGA register.</p>
Medical plausibility or scientific rationale	<p>Usually <i>in vivo</i> data.</p>	<p>Usually <i>in vivo</i> data.</p>	<p>Explanation of 'possibility of development' required by providing rationale of using the drug/medical device/regenerative medical product for the target disease, and the development plan should be reasonable.</p>	<p>Usually <i>in vivo</i> data.</p>
Alternative eligibility criteria	<p>Unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment.</p>	<p>Not profitable within 7 years following FDA approval.</p>	<p>None</p>	<p>Not likely to be financially viable for the sponsor to market the medicine in Australia unless each fee referred to in paragraph 45(12)(c) of the</p>

	EU	US	Japan	Australia
				Therapeutic Goods regulations were waived in relation to the medicine

Although the FDA and EMA do not aim for full alignment of the respective regulatory frameworks, they do engage in regular cross-talk to facilitate information sharing and to reduce variance in the review approach. At present, the collaboration between the EMA and FDA has been formalised in the EMA/FDA cluster on rare diseases. (European Medicines Agency & U.S. Food and Drug Administration, 2016)

The objectives of this cluster are to:

- Achieve a common understanding of each Agency’s regulatory approaches to rare diseases drug development as based on internal policies, guidance documents and Regulations,
- Provide a forum for discussion of candidate drugs and drug classes for the treatment of rare diseases,
- Offer a confidential forum for exchange of draft documents, policies in development, and more detailed information supporting the scientific basis for decision making, and
- Address long term safety issues and ensure a global safety net for drugs developed to treat rare diseases through confidential sharing of reports.

The Australian TGA indicates it will consider EMA orphan designation applications supported by an Australian specific annex if the content is current and relevant.⁴⁵

4.5. Marketing authorisation for EU designated orphan medicines

4.5.1. Maintenance of orphan designation

Whereas in the US and Japan orphan designation is determined only once and thereafter becomes permanent, **in the EU the designation needs to be reassessed and confirmed prior to marketing authorisation.** (Messina, Scientist, Deneux, & Science, 2016) To this end, a report justifying the maintenance of orphan status must be submitted and all qualifying criteria are reassessed. Because there are no provisions for “conditional” significant benefit and no additional data can be submitted after marketing authorisation for this purpose, **orphan designation can be at risk if only limited data are available.**

The COMP assesses whether significant benefit has been demonstrated. Whenever possible, such demonstration is built on data from Phase III randomised clinical trials (RCTs). Because Phase III RCTs are often not feasible

⁴⁵ <https://www.tga.gov.au/publication/orphan-drug-designation-eligibility-criteria>

in rare diseases, regulatory agencies allow for '*flexibility and exercise of scientific judgment in kinds and quantity of data required for a particular medicine for an indication*' (Pariser, 2014). Indirect comparisons can be accepted by the COMP on a case-by-case basis, subject to their robustness.

Separately, **the Committee for Medicinal Products for Human Use (CHMP) assesses the benefit to risk ratio in addition to evaluating "orphan similarity"**. (Commission of the European Communities, 2000c). As such, while multiple products can obtain orphan designation for the same orphan indication if they demonstrate significant benefit compared to existing designated orphan medicines, for two similar products, only the first to fulfil the conditions of marketing authorisation will be granted.

The outcomes of these assessments form the basis for the EC's decision to grant or withhold marketing authorisation with maintenance of orphan designation. This decision is binding (though it could be challenged in court) and there are no formal opposition proceedings.

4.5.2. Assessment of similarity

Article 8(1) of the EU Orphan Regulation states that, where a marketing authorisation is awarded, **another marketing authorisation for a *similar medicinal product for the same therapeutic indication, shall not be accepted for a period of ten years (or twelve for a paediatric indication)***. Commission Regulation No 847/2000 lays down the definition of the concept 'similar medicinal product'.⁴⁶

The assessment of similarity is made on the basis of the:

- Principal molecular structural features
- Mechanism of action
- Therapeutic indication

When significant differences exist within at least one of these criteria, two products will not be considered as similar.

The **2008 Guideline on aspects of the application of Article 8(1) and (3)** builds on the EU Orphan Regulation by **further explaining the assessment of similarity of medicinal products versus authorised orphan medicinal products benefiting from market exclusivity** (Commission of the European Communities, 2008a).⁴⁷ One of the additions in this guideline is that it includes a pre-emptor that not all the general considerations described under the explanation of what constitutes similar molecular structural features may be appropriate for macromolecules, particularly complex biological medicinal

⁴⁶ https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2000_847/reg_2000_847_en.pdf. The definition reads as follows: a medicinal product containing a similar active substance or substances as contained in a currently authorised orphan medicinal product, and which is intended for the same therapeutic indication", where similar active substance means "an identical active substance, or an active substance with the same principal molecular structural features (but not necessarily all of the same molecular features) and which acts via the same mechanism.

⁴⁷ <https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2008:242:0012:0016:EN:PDF>

products. Moreover, the guideline provides a set of criteria for how applications should demonstrate the proposed structure of the molecule and includes the option of using software programmes to measure the degree of structural similarity between molecules. The guideline also adds more detail on the definitions of 'pharmacological target' and 'pharmacodynamic effect'.⁴⁸

In 2017, public consultations were held on the concept of 'similar medicinal product' in response to major developments in the field of biological medicines including advanced therapy medicinal products (ATMPs).⁴⁹ The outcome of these consultations was the **publication of Commission Regulation (EC) 2018/781**, which amended Regulation (EC) No 847/2000.⁵⁰ The concept of 'similar medicinal product' remained the same, but **the definition of 'similar active substance' was changed to accommodate advanced therapy medicinal products**. Herein, a "similar active substance" is still defined as an active substance with the same principal molecular structural features and which acts via the same mechanism, if the medicinal product is a:

- Chemical medicinal product, or a
- Biological medicinal product (other than advanced therapy medicinal product)

However, for ATMPs, the similarity will instead be assessed on the basis of the biological and functional characteristics. Specific provisions were laid down also for cell-based ATMPs, gene therapy medicinal products and genetically modified cells. Radiopharmaceutical medicinal products were added as a fourth category for which the criteria to assess similarity were also included. The Amending Regulation came into force in mid-2018.

4.5.3. Relation between orphan designation and marketing authorisation

A medical product may seek to acquire marketing authorisation for more than one orphan indication. In the case of multiple orphan indications, significant benefit needs to be demonstrated separately for each. (Fregonese et al., 2018). However, under the regulatory framework (Article 4a of Regulation 847/2000) **a product cannot have a single marketing authorisation for both orphan indications and non-orphan indications**. Therefore, if the significant benefit of the second indication is not confirmed (or if the orphan designation was not applied for as the prevalence criteria are not fulfilled), the orphan designation for the first indication either must be withdrawn or a separate tradename for orphan and non-orphan indications must be used.

In many cases, the use of the product for the orphan indication would be different from the use in treatment for the non-orphan indication, as there may be differences in formulation (e.g. intravenous vs. oral) or dosage. However, in some cases the two products can be identical, as illustrated by the case in Figure

⁴⁸ Idem

⁴⁹ https://ec.europa.eu/health/human-use/orphan-medicines/developments_en

⁵⁰ <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32018R0781&from=EN>

6. In the US, there is no requirement that orphan and non-orphan indications are registered under separate marketing authorisations.

Figure 6 Illustration of requirement for separate marketing authorisations for identical products with and without orphan designation

In 2006, an EU orphan designation was granted for ciclosporin for the treatment of *vernal keratoconjunctivitis*. Since 2018, it has been available under the name *Verkazia* in the form of eye drops with 1mg/ml ciclosporin for use in children from 4 years of age and adolescents. As such, it is an identical formulation and product to the medicine *Ikervis*, which has been authorised since 2015, for the treatment of severe keratitis in adult patients with dry eye disease, a condition that is not considered an orphan condition (European Medicines Agency, 2017a).

Under the EU Orphan Regulation these two products, even though they are identical, cannot be brought to market under the same marketing authorisation. They thus require separate trade names. Both authorisations are held by Santen Oy. Neither product has been authorised by the US FDA.

A similar issue arises in case a marketing authorisation holder for a designated orphan medicine seeks to **expand or vary the therapeutic indication for which the authorisation has been granted**. This could, for instance, be the case if a product that was initially designated and approved only as a second or further line of treatment of an orphan condition is shown in clinical trials to also have a favourable effectiveness and safety profile as a first line of treatment. Since use as a first line of treatment is normally related with a larger potential treatment population, such an extension of the marketing authorisation could be very attractive to the sponsor.

In past, only the CHMP would assess extensions or variations of the marketing authorisation. However, since the 2016 Commission Notice, also the COMP needs to review whether the new therapeutic indications provide significant benefit over existing treatments. (Commission of the European Communities, 2016a) **Only if all therapeutic indications fall within the scope of the designation criteria, can the orphan designation be upheld for the product as a whole and can the sponsor maintain a single marketing authorisation.** If, however, the extended or changed indications do not meet the criteria, the sponsor must choose whether to request separate marketing authorisations for the orphan and non-orphan indications, or to withdraw the orphan designation all together.

5. State of play of the EU Orphan Regulation

5.1. Introduction

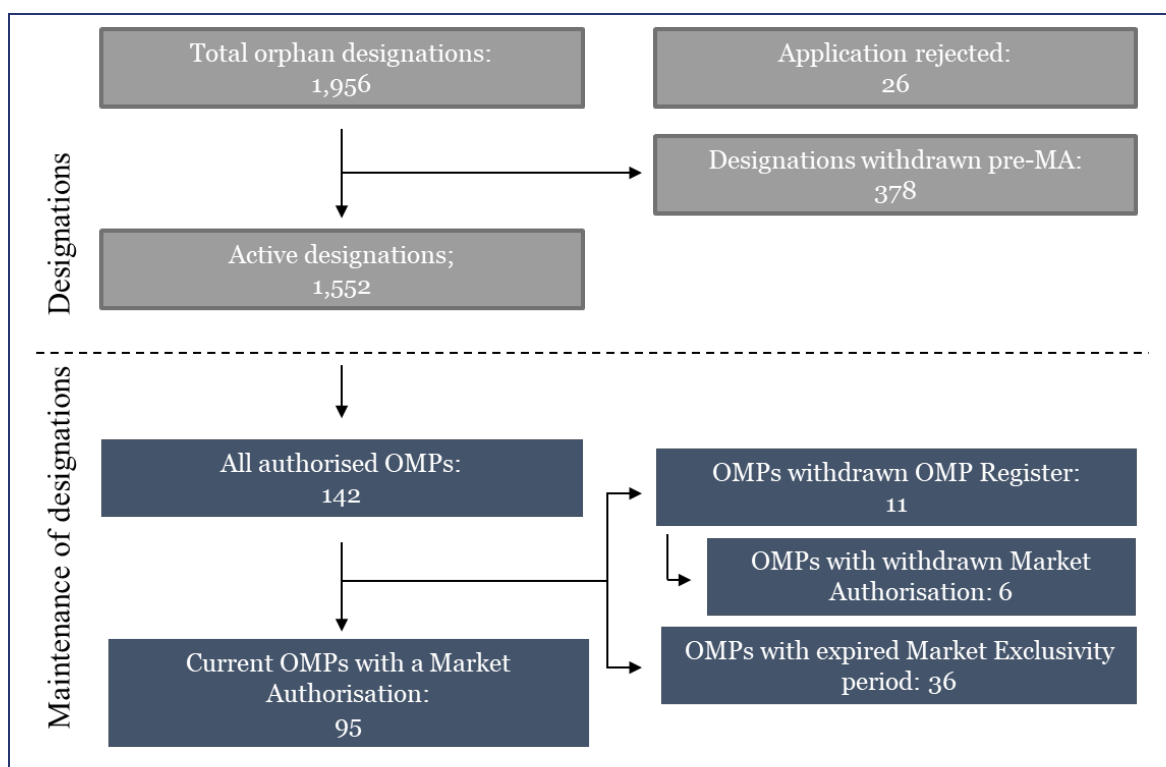
This chapter describes the state of play for orphan medicines in the EU and, selectively, in comparison with the situation in the US and other jurisdictions. It presents quantitative data, focusing on developments in the period 2000 to 2017. This chapter is descriptive in nature and provides a reference point for the subsequent analytical chapters.

5.2. EU orphan designations and authorised orphan medicines

From the moment an applicant applies for an orphan designation, there are various routes the application can take that determine whether a product receives an orphan designation and if it will ultimately reach the

market with maintenance of an EU orphan designation, should the development be successful. Figure 7 shows the flow of all applications received by the EMA between 2000 and 2017.

Figure 7 Overview of orphan designations and authorisations (2000-2017)



Source: EMA data, 2018. MA = Marketing authorisation; OMP = Orphan medicinal product

Between 2000 and 2017, a total of **1,956 designations** were granted (Figure 8). As a number of designations have since been withdrawn from the community register of orphan medicines again, there remain 1,552 active designations (i.e. for products that have ever received orphan designation and were not subsequently withdrawn from the register).

By the end of 2017, there had been **142 unique orphan medicines that received an EU marketing authorisation** and for which the orphan designation was maintained upon marketing authorisation. Several of these products have subsequently been withdrawn from the register, either because the marketing authorisation for the product was withdrawn all together or because the sponsor voluntarily opted to forego the orphan designation whilst the product maintained its marketing authorisation. For a number of products the orphan market exclusivity period had expired at the time of analysis. Therefore, the data set provided to the study team by the EMA contained **95 products that by the end of 2017 remained under active protection from orphan market exclusivity** for at least one indication. For the other products either all market exclusivity had expired, the product had been withdrawn from the market or the marketing authorisation holder had voluntarily withdrawn the product from the community register of orphan medicinal products.

Figure 8 Number of applications submitted, designations granted and authorised orphan medicines⁵¹



Source: EMA data, 2018.

The 142 authorised products included in our analysis together cover a total of **107 unique orphan indications** (see also Section 5.4.2). To estimate the total patient population in the EU that had the potential to benefit from these treatments, we used prevalence estimates provided by the product sponsor (in the case of conditions for which more than one product has been authorized, the data provided by the sponsor in the application for the most recently

⁵¹ Note: applications that were withdrawn prior to the recommendation of the COMP are not depicted. Therefore, the number of 26 'not designated' applications includes only those cases where the COMP did not recommend granting of the orphan designation

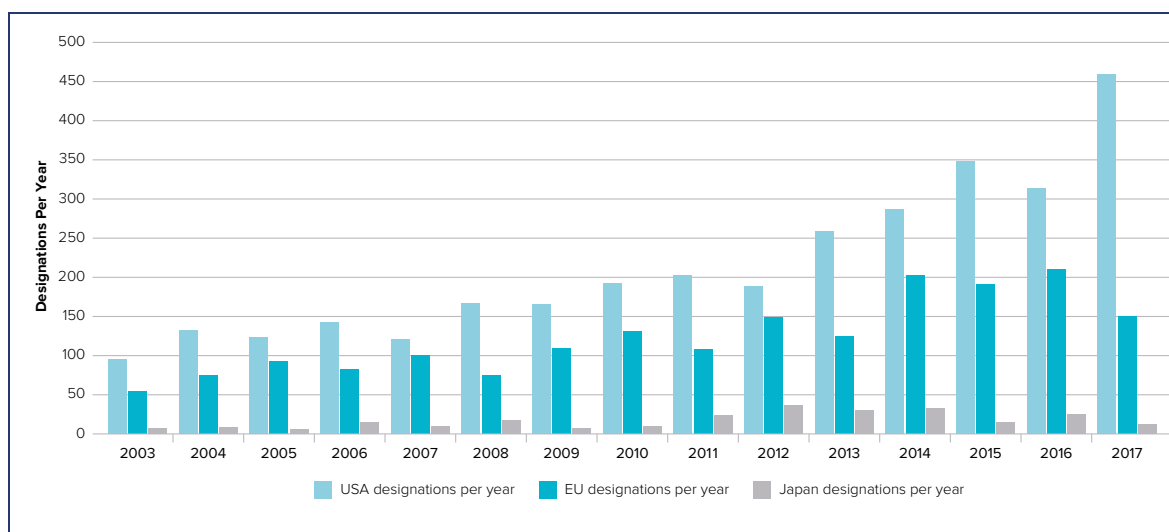
authorised product was used) and multiplied this with the EU population size at the time of authorisation. Thus, we arrive at an estimate of **around 6.3 million patients in the EU that could potentially benefit** from these 142 orphan medicines. By comparison, estimates suggest that between six to eight percent of the European population, equating to roughly 35 million people, lives with a rare disease (Dawkins et al., 2018).

To simply state, however, that the Regulation has thus helped to reduce unmet medical needs by five to seven percentage points is far too simplistic. In part, this is because **the actual treatment population is expected to be considerably smaller**, for reasons such as therapeutic indications being much narrower than the orphan indication, limited diagnostic capacity and because not all orphan medicines are marketed in all Member States (see also section 5.8). Additionally, it would assume that the development of all available treatments can be attributed to the EU Orphan Regulation. This would ignore the reality that the EU Orphan Regulation exists alongside a variety of other regulatory frameworks (such as those in the US and Japan) and initiatives to support the development of orphan medicines.

5.2.1. Comparison to orphan designations and authorisations in other jurisdictions

The continued increase in the number orphan designations reflects the **industry's increasing interest in developing orphan medicines**. This trend is not limited to the EU but is seen in other jurisdictions as well. In 2017, the FDA granted 459 orphan drug designations, an increase of 43% from 2016 (Figure 9) (EvaluatePharma, 2018). This sharp increase has been attributed, at least in part, to the implementation of the orphan drug modernisation plan by the FDA⁵², which aims to eliminate the backlog of existing designation requests and to ensure a timely review of new applications. Whilst that year the number of designations granted in the EU was in fact smaller than in previous years, **overall there is a clear upward trend in both the US and EU**. In Japan, the annual number of designations is more stable and considerably below that of the other two jurisdictions. This reflects a difference in approach, as in Japan designations are only granted where there is judged to be a high likelihood of successful development.

⁵² <https://www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/orphan-drug-modernization-plan>

Figure 9 Annual number of designations in US, EU and Japan (2003-2017)

Source: EvaluatePharma Orphan Drugs Report 2018

Not only the number of orphan designations has grown sharply over time in all three jurisdictions, but also the number of authorised orphan medicines. In 2017, 37% (13 of 35) of new active substances recommended by the EMA for authorisation had an orphan designation (European Medicines Agency, 2017d). That same year, in the US, 39% (18 of 46) of the novel medicines approved by the FDA had an orphan designation (U.S. Food and Drug Administration Center for Drug Evaluation and Research, 2018).

Compared to the EU, the US shows both a higher annual number of designations and of marketing authorisations for orphan medicines. In part, these higher numbers may be accounted for by differences in the eligibility criteria, most notably the somewhat higher prevalence threshold that is used in the US (Table 3, Section 4.4). It may also partially reflect the fact that the US has a larger pharmaceutical industry with more developers of orphan medicines. However, it should be emphasised here that, in both the EU and US, the regulatory frameworks do not limit who can apply for orphan designation based on the geographic origins of the company.

In respect to the number of authorised orphan medicines, a further possible contributing factor is the two-stage process used in the EU whereby eligibility for orphan designation needs to be confirmed at the time of the marketing authorisation. However, the EMA did not provide the study team with quantitative information on how many products 'lost' their initial EU orphan designation at the time of authorisation as a direct result of it no longer meeting the eligibility criteria. Furthermore, in the absence of information for which products orphan designation was not maintained, it could not be established which of these were still brought to market as an orphan medicine in the US, where confirmation of orphan designation is not required. **It is therefore not possible to state what the impact of the requirement for maintenance of orphan designation in the EU is on the number of medicines brought to market for the treatment of rare diseases.** Stakeholder consultations

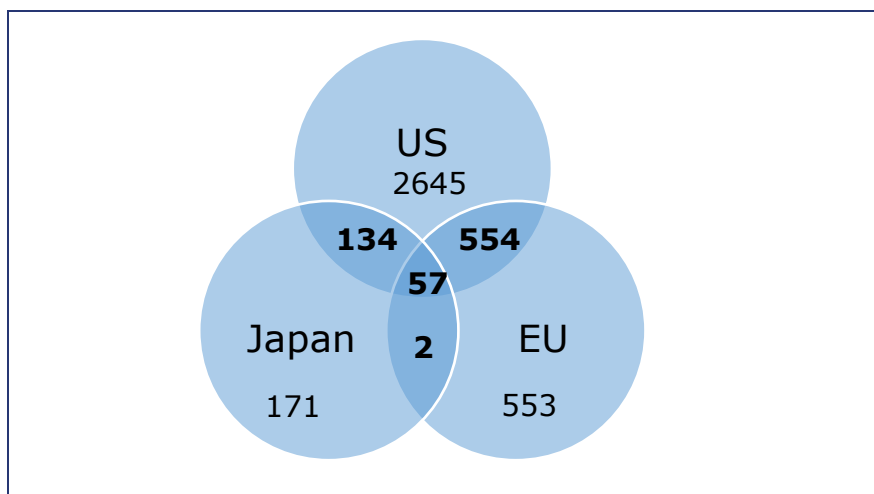
provided no indications that developers consider the two-stage process in the EU a significant deterrent to the development of orphan medicines. Representatives of the FDA, in an interview, suggested that the introduction of a similar confirmation step has been under discussion in the US but that there currently are no plans to do so. It was also indicated that, even if it is known that between the time of the orphan designation and the marketing approval of a product, the product has lost its eligibility (for instance, because prevalence has increased) the designation is not removed as long as the sponsor is believed to have acted in good faith and with the best available information at the time.

The conversion rate of initial designation into an authorised orphan medicine differs markedly across the regions. A study by Murakami and Narukawa showed that the percentage of successful marketing approvals to orphan drug designations was 15% in the US, 8% in the EU and 65% in Japan (Murakami & Narukawa, 2016). The high approval/designation ratio in Japan is consistent with the approach to designate only products with a high chance of approval. Whilst no information was reviewed to explain the difference between the EU and US, it may be attributable in part to the fact that the regulatory framework in the EU uses a two-staged process, whereby orphan designation needs to be confirmed at the time of marketing authorisation. This extra requirement could mean that, even when the overall success rate for products getting to marketing authorisation is similar, the number of products that do so with an orphan designation is lower in the EU.

The same study also compared orphan designations granted until 28 February 2015 in the EU, Japan and the US, using a matched data set⁵³. This data set included 747 designations common to two or three of the jurisdictions (Figure 10). (Murakami & Narukawa, 2016) This analysis shows **there is considerable overlap between the frameworks, with 53% of EU designations also designated in the US.** The ration was similar for authorised orphan medicines, with 49% of EU authorised orphan medicines also having been approved in the US. The overlap in designations between the EU and Japan is considerably smaller, with only 5% of EU designations matched in Japan. This again reflects the difference between the two frameworks. The study does not present data to compare authorised orphan medicines in the EU and Japan.

⁵³ The authors created a matched data set by pairing medicines in each region with medicines in other regions based on the brand name, applicant name, and proposed indication. To be included in the data set, a medicine would need to be designated in at least 2 of the 3 jurisdictions. As the regulatory frameworks were introduced in 1983 (US), 1993 (Japan) and 2000 (EU) respectively, this effectively limits the analysis timeframe to the period 1993-2015 (28 February).

Figure 10 Matched orphan designations in the US, EU and Japan



Source: Adapted from Murakami & Narukawa 2016. Shown in bold are designations common to 2 or 3 of the jurisdictions.

5.3. Uptake of the incentives offered by the EU Orphan Regulation

5.3.1. Market exclusivity

In the period 2000-2017 in total 142 orphan medicines were authorised with maintenance of orphan designation, thereby triggering the market exclusivity. Of these, 12 were subsequently withdrawn from the Community Register of designated Orphan Medicinal Products after marketing authorisation such that they did not complete the full term of the market exclusivity.

As will be shown further in Section 5.6, 20 products have been authorised for more than one orphan indication, and a separate period of market exclusivity was granted for each of those orphan indications (46 orphan indications). **In total, market exclusivity was granted 168 times.**

5.3.2. Fee waivers

All orphan medicine developers are eligible for reduced fees (fee waivers) for protocol assistance, marketing authorisation applications, inspections, changes and annual fees from the EMA (Table 4).

Table 4 Fee reductions for designated orphan medicines

Procedure or service	Applicable to	Reduction
Protocol assistance, initial and follow-up requests	SME sponsors for all assistance	100%
	Non-SME sponsors for non-paediatric-related assistance	75%
	Non-SME sponsors for paediatric-related assistance	100%
Pre-authorisation inspection	All sponsors	100%
Initial marketing authorisation application	SME sponsors	100%
	Non-SME sponsors	10%
Post-authorisation applications and annual fee, specified in Council Regulation (EC) No	SME sponsors	100%

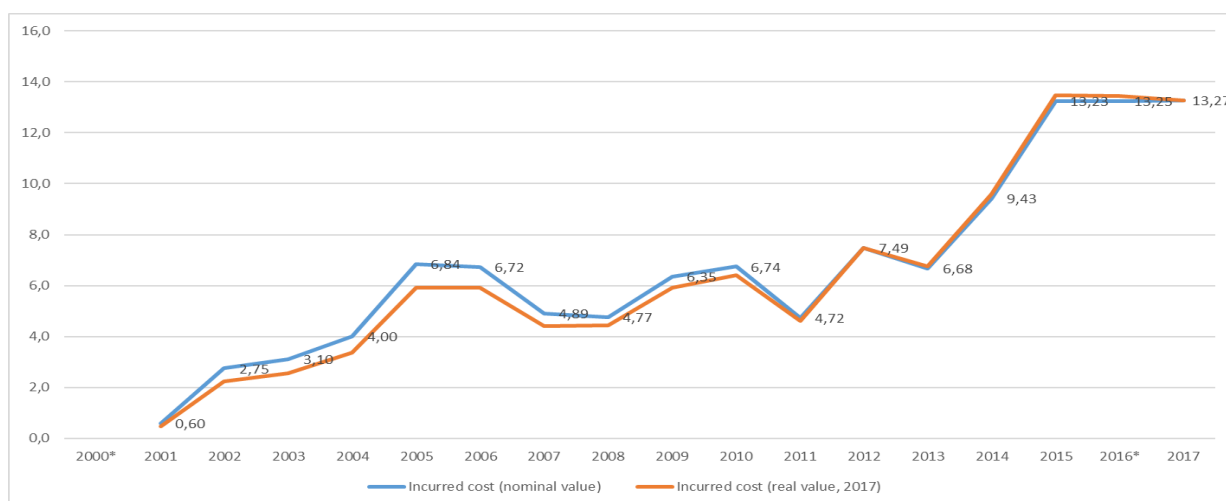
297/95, in the first year from granting of a marketing authorisation		
Pharmacovigilance fees, specified in Regulation (EU) 658/2014	All sponsors	n/a

Source: EMA (2014), 'Executive Director's decision on fee reductions for designated orphan medicinal products'. (Applicable on October 2018). (European Medicines Agency, 2017c).

The EMA reports every year on the fee reductions for designated orphan medicines, which are funded from the special contribution from the EU.

Figure 11 shows the development of the costs of these fee reductions over the period 2000-2017, both in nominal and real value (price level 2017). For the total period, the nominal costs are approximately €114m.

Figure 11 Reported value fee reductions for designated orphan medicines (€ million, 2000-2017)

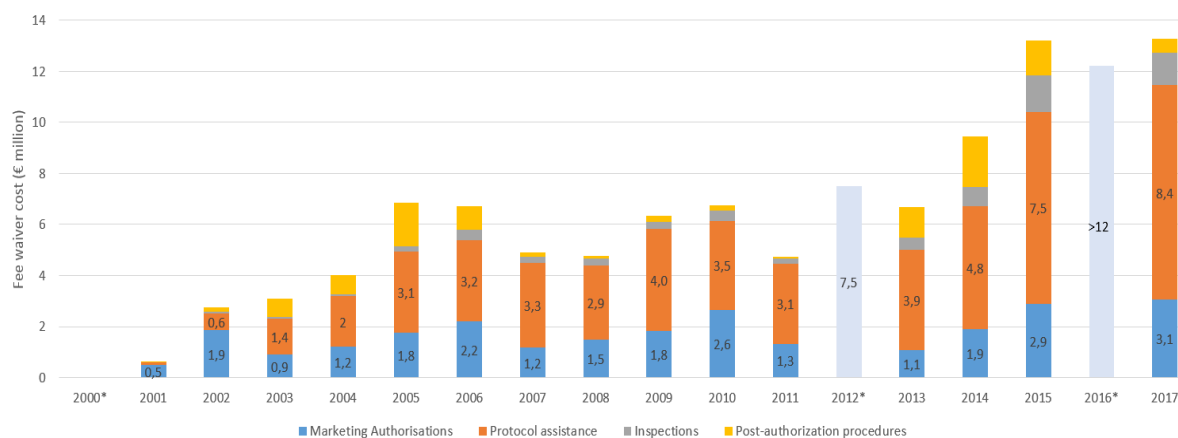


Source: EMA, annual reports. Note: for 2016 the total value is not given, now based on average 2015/2017. The information for 2000 was not comparable to the other years.

The EMA reports also detail the breakdown of the costs for various categories, specifically reductions on the fees for (i) marketing authorisations, (ii) protocol assistance, (iii) inspections and (iv) post-authorisation procedures (

Figure 12). Reductions on the fees for protocol assistance is the largest cost category (over the total period approximately 55% of the total costs), followed by fee reductions on marketing authorisations (27% over the total period).

Figure 12 Breakdown of the fee waiver costs for orphan medicines by year (€ million, nominal value, 2000-2017)

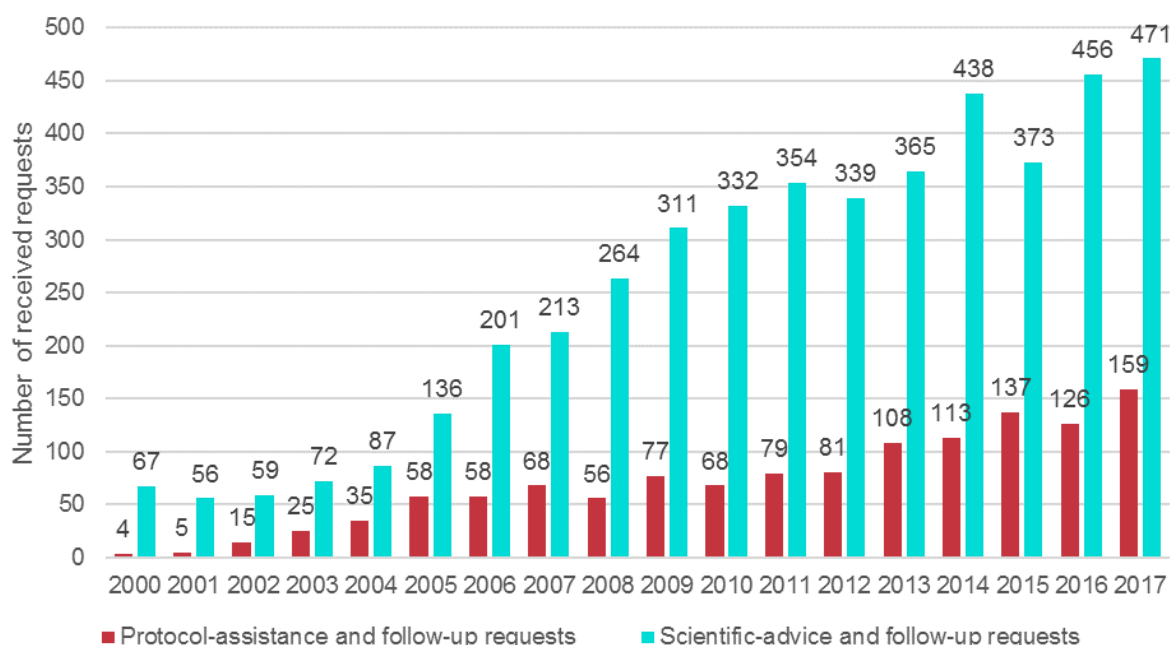


Source: EMA, annual reports. Note: The information for 2000 was not comparable to the other years; for 2012 and 2016, the breakdown is not provided in the annual report.

5.3.3. Protocol assistance

The EMA annually reports the number of requests for scientific advice and protocol assistance. Over the period 2000-2017, there was a significant increase in the number of annual requests for both scientific advice (factor 7) and protocol assistance (Figure 13).

Figure 13 Overview use protocol assistance (2006-2017)

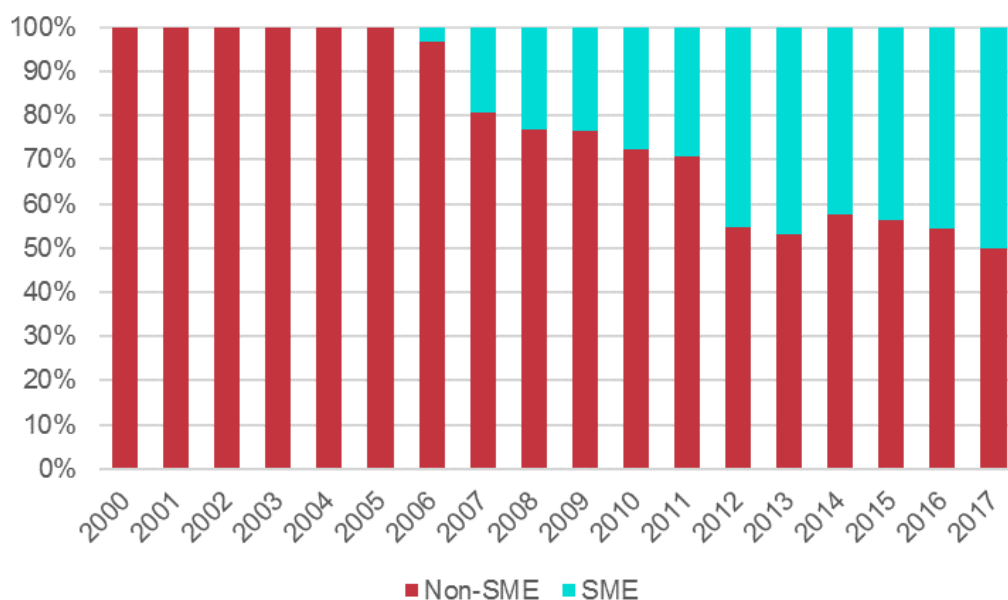


Source: EMA annual reports 2000-2017.

In addition, the EMA provided the study team non-public data on the type of users, i.e. whether a user is an SME or not. This data shows that over the period 2000-2017 both the (absolute) number of protocol assistance requests from

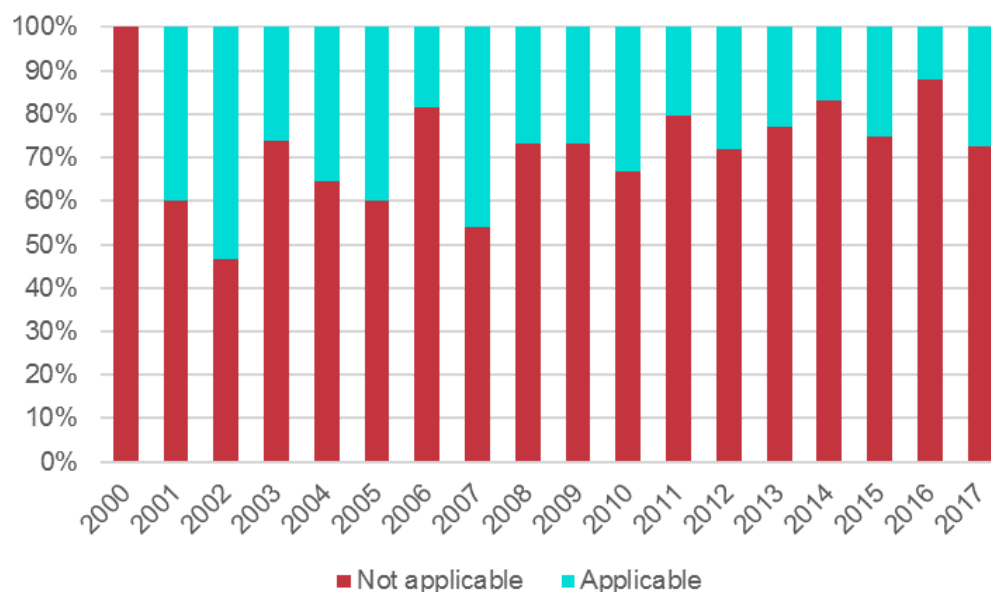
SMEs and the relative share of SMEs (as percentage of total) increased. (Figure 15).

Figure 14 Share of SMEs in total number of protocol assistance requests (in % of total, 2000-2017)



Source: EMA; non-public data. Note: the total number of listed entries in the data in this period is 1,262.

EMA also provided data on whether the request was related to the demonstration of significant benefit. Although the numbers vary per year but, over the period 2000-2017, this applied in approximately 26% of cases. (Figure 16)

Figure 15 Share applicability 'demonstration of significant benefits' (in % of total, 2000-2017)

Source: EMA; non-public data. Note: the total number of listed entries in the data in this period is 1,250.

5.4. Characteristics of EU designated and authorised orphan medicines

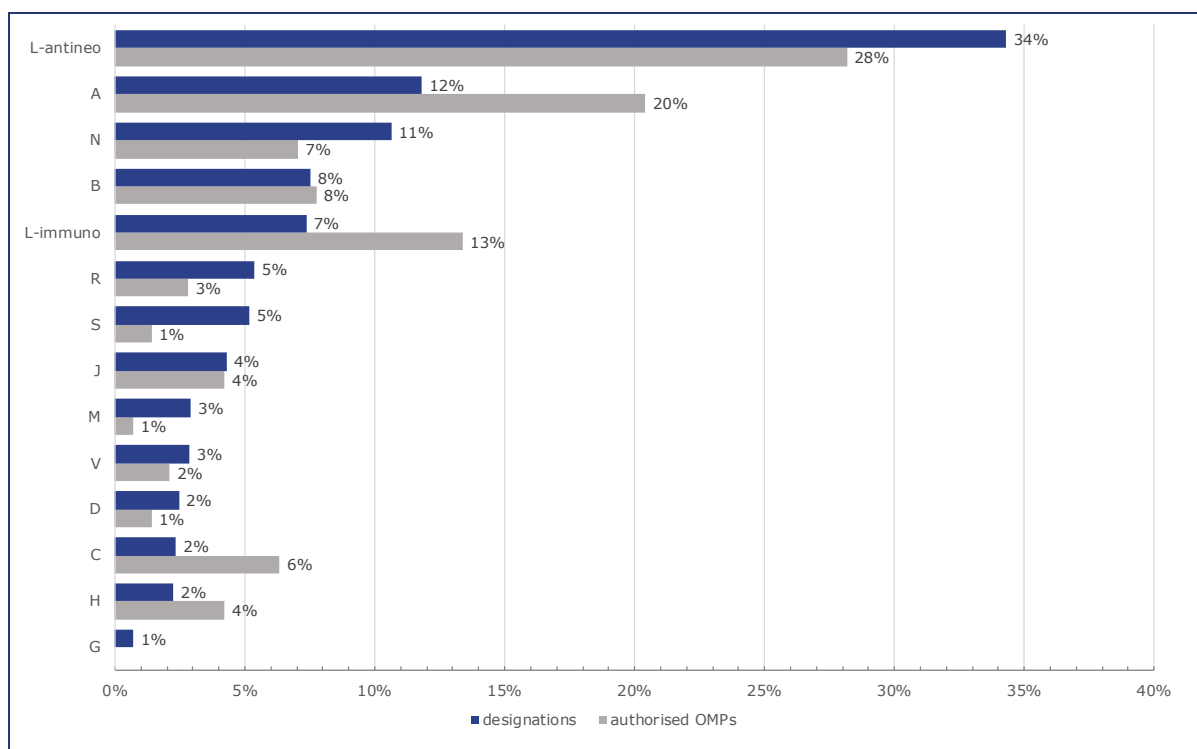
5.4.1. By therapeutic area

The portfolio of both designations and authorised orphan medicines was analysed using the Anatomical Therapeutic Chemical (ATC) Classification System, similar to what was done previously for the products for treatment of rare diseases on the market before 2000 and 'orphan-like' products (Section 2.2).

Among both designations and authorised products, **the largest share of products (28-34%) belongs to the class of 'antineoplastic agents' (part of ATC code L), which consists primarily of anti-cancer treatments.** This is, at some distance, followed by treatments for conditions of the alimentary tract and metabolic disorders (ATC code A, 12-20%) (Figure 16). Despite a small number of designations, no products have been authorised yet in the category of genito-urinary tract conditions and sex hormones (ATC code G), nor of anti-parasitic products (ATC code P).

Figure 16 Number and share of orphan designations and authorised orphan medicines by ATC code

	L-ant	A	N	B	L-imm	R	S	J	M	V	D	C	H	G	Total
Designated	671	231	208	147	144	105	101	84	57	56	48	46	44	14	1,956
Authorised	40	29	10	11	19	4	2	6	1	3	2	9	6		142

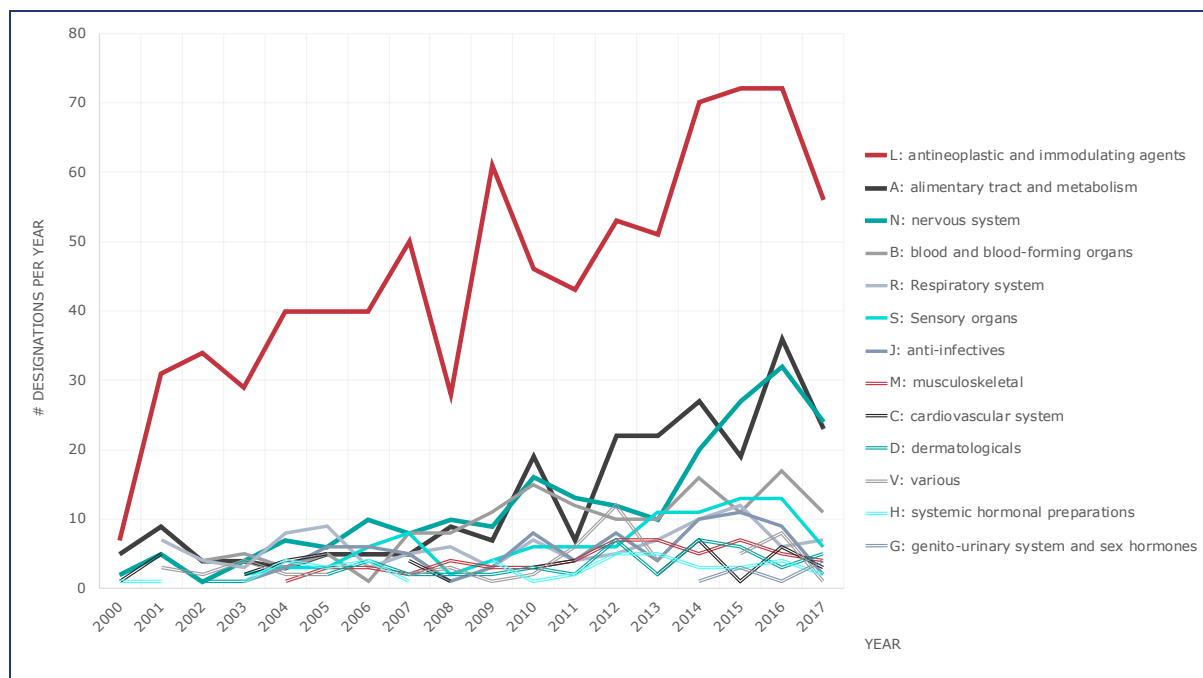


Source: EMA, 2018. Includes data up to end 2017. L-antineo = antineoplastic agents, A = alimentary tract and metabolism, N = nervous system, B = blood & blood-forming organs, L-immuno = immunomodulating agents, R = respiratory system, S = sensory organs, J = anti-infectives, M = musculoskeletal, V = various, D = dermatological, C = cardiovascular, H = systemic hormonal preparations, G = genito-urinary system & sex hormones.

The annual number of designations has been relatively stable in most areas (mostly no more than 10 per year), with a few notable exceptions (Figure 17):

- Antineoplastic and immunomodulating (anticancer) agents (ATC code L) have increased from 30-40 designations per year in the period 2001-2006 to well over 50 designations annually from 2012 onwards. The share has stabilised in the last 3-4 years.
- Designations for products targeting conditions of the alimentary tract and metabolism have more than tripled since 2010.
- Designations for conditions of the nervous system, such as Huntington’s disease, have seen a similar sharp increase in the last 5 to 10 years.

Figure 17 Annual orphan designations by ATC code



Source: EMA, 2018. Includes data up to end 2017.

A 2016 study found that in the US and Japan oncology and immunomodulatory medicines also accounted for 30-40% of all designations, but that in Japan there was a higher number of infectious disease designations compared with the EU and US (Murakami & Narukawa, 2016).

5.4.2. By orphan indication

Although the aforementioned analysis by ATC is useful to understand in broad terms where R&D activity is seen most, a more fine-grained analysis is needed to appreciate the overall coverage of rare conditions offered by products designated under the EU Orphan Regulation. Hereto the portfolio of designated and authorised products was analysed using the information on the orphan indication as provided by the EMA⁵⁴.

In total, **the 1,956 designations analysed covered 698 unique indications**. These included 637 (91%) treatments, 53 (8%) products for prevention⁵⁵, and 8 (1%) products used in diagnosis.

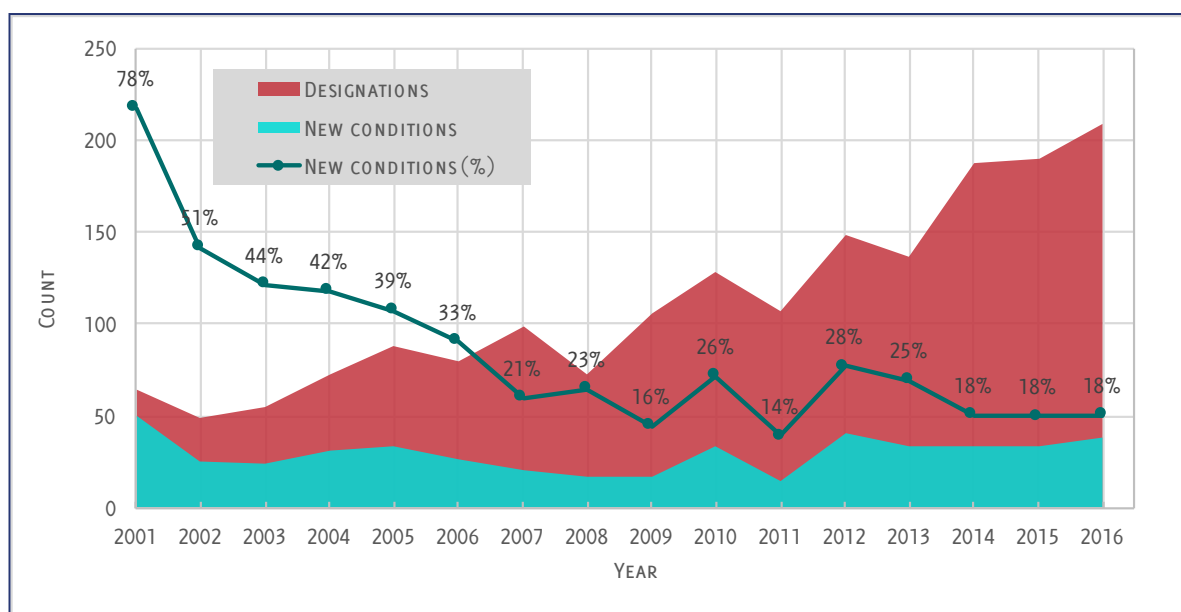
⁵⁴ Information on the indication is entered manually into the EMA system. Therefore, inconsistencies and spelling variations and errors have occurred. Although we have cleaned the data as best as possible to correct for these, it remains possible that some entries have been counted as corresponding to separate indications when, in fact, they are for the same indication. This will be primarily the case for indications where some entries have been more detailed than others.

⁵⁵ Prevention herein includes both prevention of disease (e.g. prevention of tuberculosis disease in BCG vaccinated individuals) and prevention of complications as a result of existing disease (e.g. prevention of graft rejection after transplantation, or sepsis after surgery).

Among **142 authorised orphan medicines, in total 107 unique orphan indications are covered**. All of these concern treatments (105, 98%), except for 2 products used in cancer diagnosis.

In the years immediately after the Regulation’s introduction, the **number of new orphan indications targeted per year has declined** rapidly (Figure 18). Whereas in 2001 78% of orphan designations were for new indications (i.e. for which no other treatment existed), in recent years this has **decreased to less than one in five designations**.

Figure 18 New indications targeted in relation to overall number of products that received orphan designation

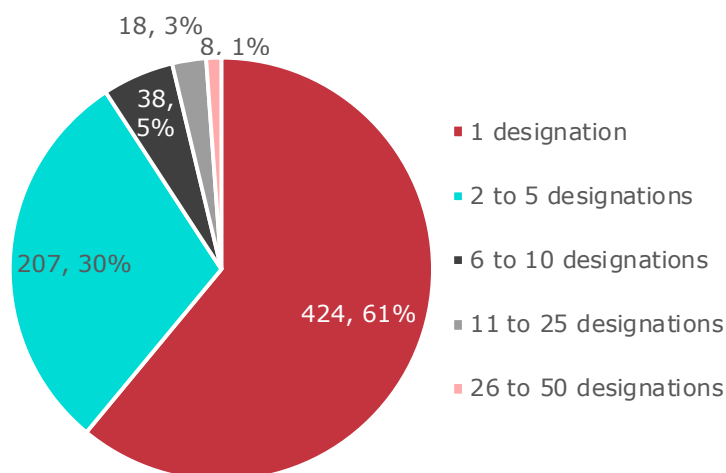


Source: EMA data, 2018.

Analysis of EMA data shows that overall, of the orphan medicines authorised between 2000 and 2017, only **28% of all authorised orphan medicines did not need to demonstrate significant benefit** because they targeted diseases for which there were no alternative treatment options.

Analysis of all designations shows that **even within certain orphan indications, there can be a high degree of activity** (Figure 19). For instance, there are 74 designations for treatment of *acute myeloid leukaemia* alone. Other areas where there is high activity are *glioma* (56 designations), *cystic fibrosis* (51 designations), *pancreatic cancer* (47 designations), *ovarian cancer* (40 designations), *multiple myeloma* (32 designations) and *Duchenne muscular dystrophy* (31 designations). However, for 61% of all unique orphan indications there is only one designated product.

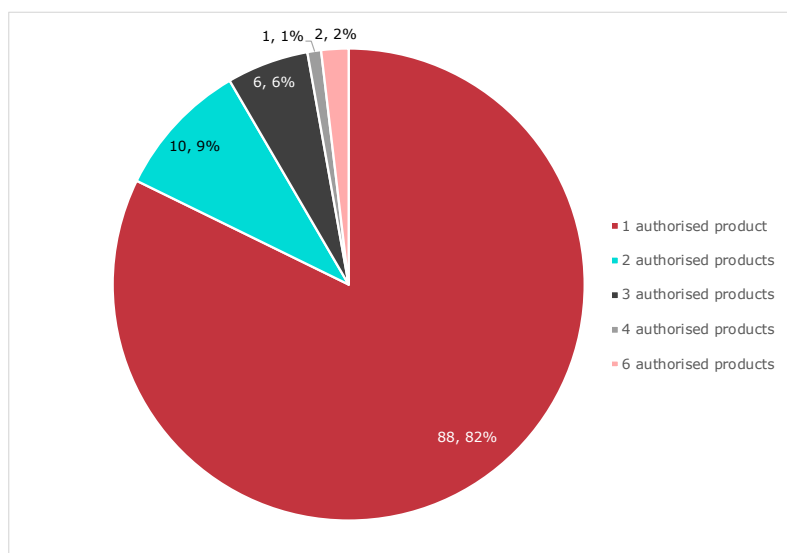
Figure 19 Number of orphan designations within a single orphan indication



Source: EMA data, 2018.

Within the portfolio of authorised orphan medicines too, some clustering around orphan indications is observed (Figure 20). For *acute lymphoblastic leukaemia* and for *multiple myeloma* 6 products each have been authorised. Strikingly, out of the 9 unique orphan indications for which 3 or more products have been authorised, 4 are a form of blood cancer⁵⁶. For the vast majority (88, 82%) of orphan indications for which products have been authorised, though, just a single product has been launched.

Figure 20 Number of authorised orphan medicines per orphan indication



Source: EMA data, 2018.

⁵⁶ Acute lymphoblastic leukaemia (6), multiple myeloma (6), acute myeloid leukaemia (3), chronic lymphocytic leukaemia (3) and chronic myeloid leukaemia (3).

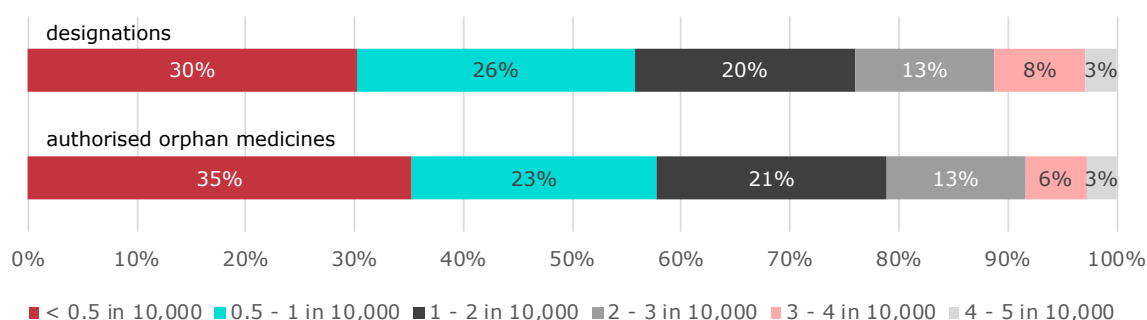
5.4.3. By prevalence of orphan conditions

The idea behind the introduction of the EU Orphan Regulation has been to incentivise product development for some of the rarest conditions, where the expectation of return on investment is lowest due to the small patient base. To see whether this has indeed happened, an analysis was performed of the portfolio of designations and authorised orphan medicines, using information on the estimated prevalence of the orphan indication.

Overall, the distribution by prevalence is very similar among designated and authorised products (

Figure 21). In both groups, **around a third of products are for treatments with a prevalence of less than 0.5 in 10,000**. These are mainly products for treatment of diseases affecting the musculoskeletal system, but also some rare forms of cancer. The share of products decreases with increasing prevalence. Only three authorised treatments are for conditions with a prevalence approaching the threshold for eligibility⁵⁷.

Figure 21 Share of designations and authorised orphan medicines by disease prevalence



Source: EMA data, 2018.

The here presented analysis has been done on the basis of individual designations. Therefore, products that have received multiple designations are included here according to the prevalence rate for each of the respective orphan indications rather than by cumulative prevalence across all such indications. Products author

5.4.4. By type of product

Since the introduction of the EU Orphan Regulation in 2000, there have been some important developments in the 'types' of products being developed. Whereas in the past, the large majority of medicines were small molecules, prepared through chemical synthesis or extraction, nowadays many new treatments are based on so-called 'biologicals'⁵⁸: proteins, antibodies or other

⁵⁷ For treatment of narcolepsy, neurotrophic keratitis, and hypoparathyroidism.

⁵⁸ Part A of Council Regulation (EEC) No 2309/93 defines biologics as "Medicinal products developed by means of one of the following biotechnological processes: 1) recombinant DNA technology, 2) controlled expression of genes coding for biologically active proteins in prokaryotes

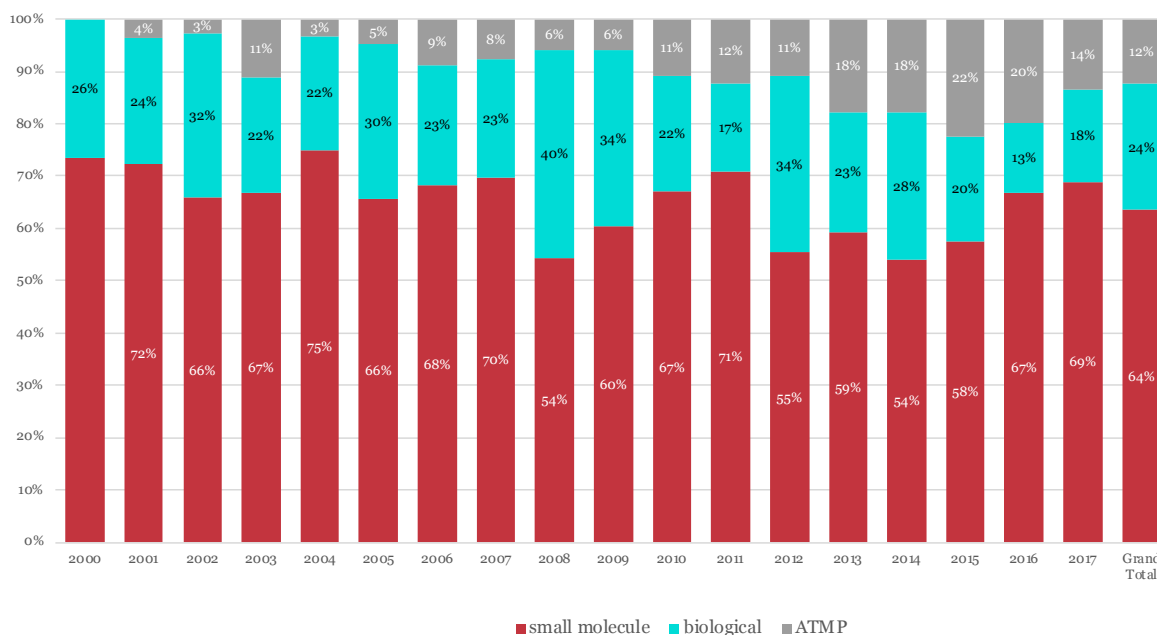
large molecules, which are produced using biotechnology. More recently, we have also seen the emergence of a new class of products that are based on techniques such as gene therapy, somatic cell therapy and tissue engineering. These are collectively known as '**advanced therapy medicinal products**' (ATMPs).

We performed an analysis of the portfolio of orphan designations and authorised orphan medicines, by classifying all products into three broad product types: small molecule medicines; biologicals; and advanced therapies. The share of biological products has remained relatively stable, at around a fifth of all designations (Figure 22).⁵⁹ Of these, 32 (23%) have thus far been authorised. **The share of ATMPs, meanwhile, has sharply increased to around 18-20% of all new designations in the period 2013 – 2016, with a small decline (14%) in 2017.**⁶⁰ By the end of 2017, four ATMPs that had been designated as orphan medicines had been authorised (Glybera, Holoclax, Strimvelis, and Zalmoxis).

and eukaryotes including transformed mammalian cells, or 3) hybridoma and monoclonal antibody methods."

⁵⁹ Products that, based on the information provided regarding the active substance, were identifiable as proteins (e.g. containing suffixes such as -ase, -mab or key words such as protein, antibody or immunoglobulin or recombinant) or that were listed as 'protein based therapies' on <http://www.drugbank.ca> were classified as biological, unless information was available that products were synthetic in origin. Fusion products that were produced at least in part through a biological process were also considered biological. Additionally, cell extracts and whole cell cultures were included. Polypeptides less than 40 amino acids in size were all classified as small molecules. Whilst the general classification approach was discussed with the EMA, the classification of individual products has not been independently validated by the EMA or other scientific experts.

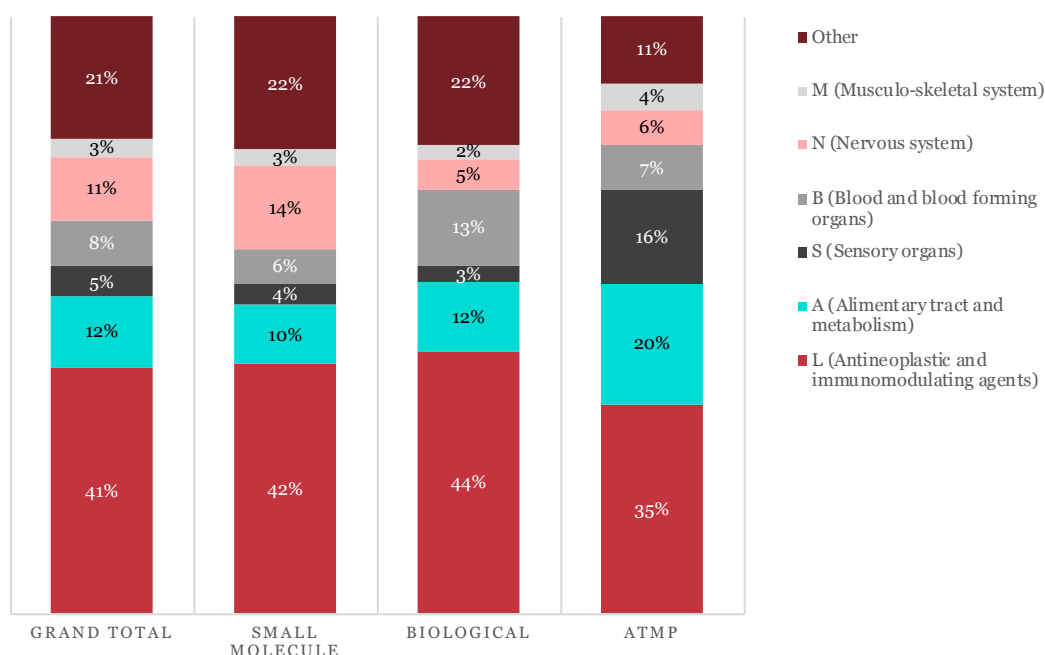
⁶⁰ Products that, based on the information provided regarding the active substance, were identifiable as proteins (e.g. containing suffixes such as -ase, -mab or key words such as protein, antibody or immunoglobulin or recombinant) or that were listed as 'protein based therapies' on <http://www.drugbank.ca> were classified as biological, unless information was available that products were synthetic in origin. Fusion products that were produced at least in part through a biological process were also considered biological. Additionally, cell extracts and whole cell cultures were included. Polypeptides less than 40 amino acids in size were all classified as small molecules. Whilst the general classification approach was discussed with the EMA, the classification of individual products has not been independently validated by the EMA or other scientific experts.

Figure 22 Orphan designations by type of product

To understand where most value is offered by these relatively new types of products, we also analysed the relative composition of each class of products by ATC code (Figure 23). Comparison between designations for small molecules and for biologicals shows few significant differences. Both types of products have a significant share of anti-cancer treatments (42% and 44% respectively). The main difference here is that biologicals are somewhat more frequently targeted at conditions affecting blood and blood forming organs than small molecules (13% and 6%), whereas the opposite is found for conditions affecting the nervous system (5% and 14% respectively).

A more striking difference can be seen between small molecules on the one hand and ATMPs on the other. **Among designations for ATMPs, relatively large shares of products are found that target conditions affecting the sensory organs** (4% of small molecules versus 16% of ATMPs) and **alimentary tract and metabolism** (10% and 20% respectively). Our findings are consistent with a recent analysis by Farkas et al. (Farkas et al., 2017). It is not known whether these differences can be attributed to the specific nature of ATMPs and the conditions targeted, or to other parameters such as alignment with existing product portfolios of developers.

Figure 23 Orphan designations by ATC code and type of product



5.4.5. By target population

As noted previously, rare diseases often are genetic in origin and manifest already in childhood. To see whether the current pipeline of treatments adequately reflects this reality, we performed an analysis of all designations and authorised orphan medicines by target population. We conducted two separate sets of analyses.

The first analysis looked at the population affected by the orphan indication of the product. We find **that 76% of all designations are for conditions that affect (also) children** (Table 5). The distribution is nearly identical for authorised products: at the time of analysis, 111 products (78%) were authorised for conditions that affect (also) children.

Table 5 Number and share of designations and authorised orphan medicines by target population

Population affected by the condition	Designated	%	Authorised	%
Adult & paediatric	1,324	68%	97	68%
Only paediatric	166	8%	14	10%
Only adults	466	24%	31	22%
Total	1,956		142	

Source: EMA, 2018.

To better understand for what types of conditions medicines with potential application for children are being developed, these numbers were further broken down by ATC code (

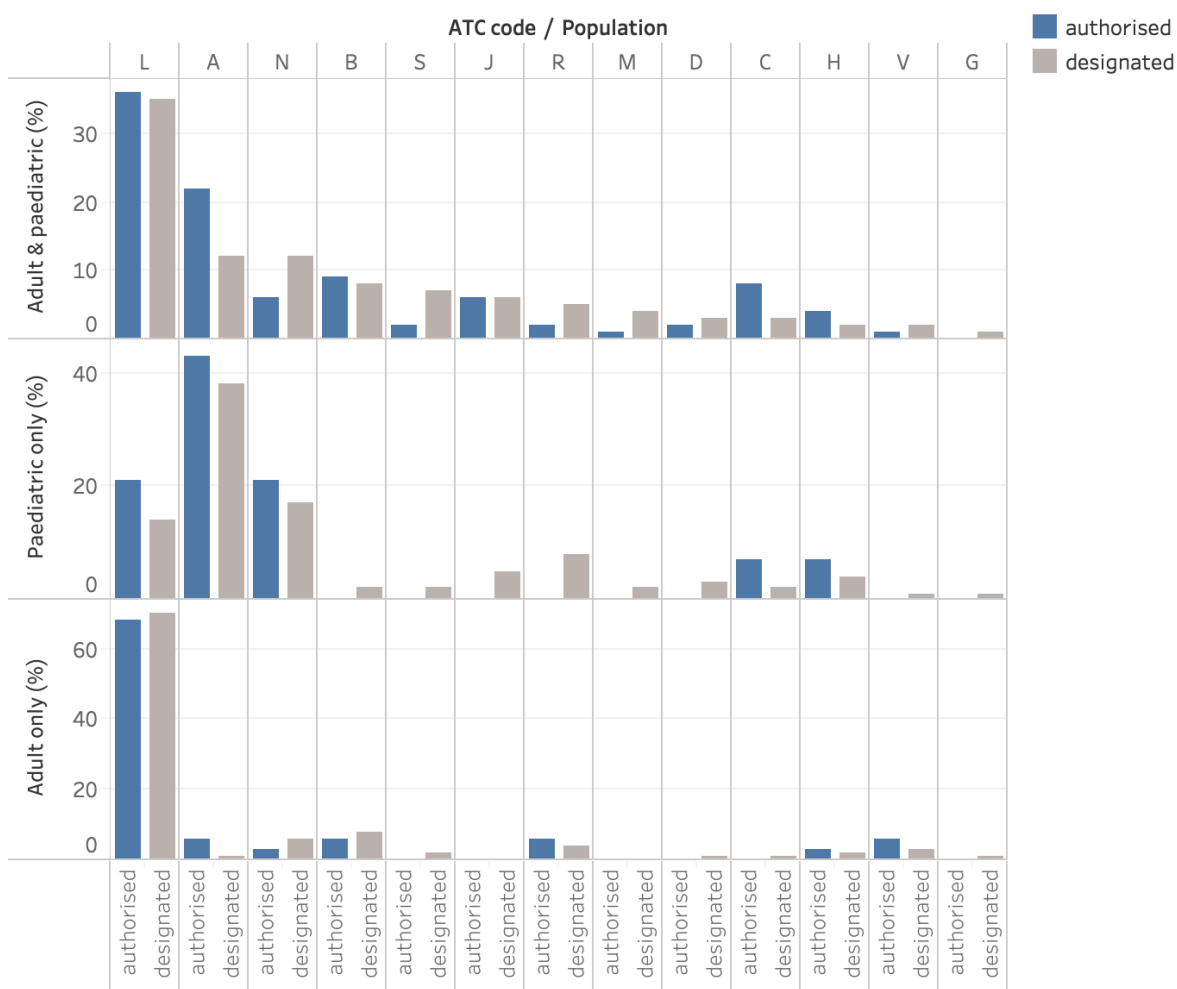
Figure 24):

- Products developed for **conditions that exclusively affect children** (166 designations, 14 authorised products): Products for this group of patients **most commonly target diseases affecting the alimentary tract and metabolic disorders** (63 designations; 6 authorised products) Many of these products are for inherited enzyme deficiency diseases, which often have a poor prognosis. Products are also being developed to treat paediatric-only forms of cancer (24 designations, 3 authorised products⁶¹) and paediatric-only conditions of the nervous system (28 designations, 3 authorised products).
- Products developed for **conditions that affect both children and adults** (1,324 designations, 97 authorised products): Here, the **highest share of products are anti-cancer medicines** (464 designations, 35 authorised products). However, as in the first group, treatments for alimentary tract conditions and metabolic disorders are also relatively common (164 designations, 21 authorised products). This includes treatments for conditions such as Fabry disease and Gaucher disease.
- **Anti-cancer treatments are even more dominant** among products developed for **conditions that affect only adults** (327 of 466 designations, 21 of 31 authorised products). In none of the other therapeutic areas are more than 2 products authorised.

This breakdown shows that development of products with the potential to benefit children has tilted heavily to just a few therapeutic areas: 60% (896 of 1,490) of designations and 66% (74 of 111) of authorised products fall into the categories with ATC codes L (anti-cancer treatments), A (alimentary tract and metabolic disorders) and N (nervous system). **In total, 38 products have been authorised for forms of cancer that affect (also) children.**

⁶¹ However, one product (Unituxin) has since been withdrawn from the market by the marketing authorisation holder due to short- and intermediate- term inability to supply it in sufficient quantities for meeting global demands and is no longer available. (https://www.ema.europa.eu/en/documents/public-statement/public-statement-unituxin-withdrawal-marketing-authorisation-european-union_en.pdf)

Figure 24 Therapeutic indications by patient population group for orphan medicines



Source: EMA data, 2018. L = antineoplastic & immunomodulating agents, A = alimentary tract and metabolism, N = nervous system, B = blood & blood-forming organs, S = sensory organs, J = anti-infectives, R = respiratory system, M = musculoskeletal, D = dermatological, C = cardiovascular, H = systemic hormonal preparations, V = various, G = genito-urinary system & sex hormones.

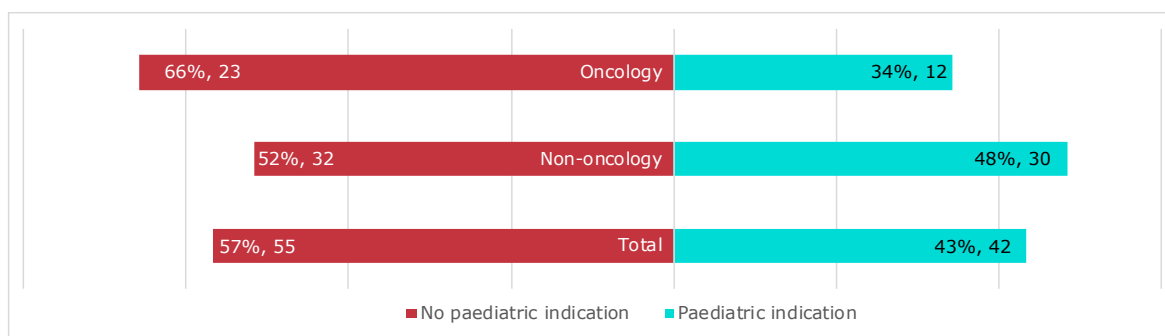
Whilst these analyses show that a substantial number of treatments are being developed for conditions that affect children, this alone does not guarantee that those products can in fact be used in this population. Products can, in principle,⁶² be used to treat to children only when this population is included in the therapeutic indication (rather than the orphan indication). This information is contained in the Summary of Product Characteristics (SmPC). To assess to what extent products have been demonstrated to be safe and effective in children, the therapeutic indication of all 111 authorised products for conditions affecting (also) children was reviewed.

⁶² It is, however, not uncommon for medicines to be used to treat children even when this use has not been included in the therapeutic indication (off-label treatment).

Alongside the 14 authorised orphan medicines for paediatric-only indications, 42 products for conditions affecting both adults and children contained a therapeutic indication for paediatric use in the SmPC. Thus, overall, of the 111 included products **56 authorised orphan medicines were approved for use in children (50%)**. This includes 15 anti-cancer treatments. Three products have since been withdrawn from the market, such that at the time of analysis **53 orphan medicines remained on the market with a paediatric use indication**.

To see whether there is any difference in paediatric development between therapeutic areas, we also analysed for which types of products paediatric indications have been included if conditions affect both children and adults. In most therapeutic areas, the total number of authorised products for such conditions is rather small⁶³. Comparison across all individual therapeutic areas would therefore provide a rather distorted picture. Instead, our comparison has focused on oncological products⁶⁴, the largest class of products, versus the rest of the product portfolio (Figure 25). **Oncological products are somewhat less likely to have a paediatric use indication than non-oncological products overall** (34% vs 43% respectively).

Figure 25 Authorised orphan medicines with a paediatric use indication for conditions affecting adults and children by therapeutic area



Paediatric use indications can be, and often are, added after the initial marketing authorisation when the studies mandated by the PIPs have been completed. One could thus expect that products that have been authorised longer ago more often have a paediatric use indication than products that have only recently been authorised. To test whether this effect is visible we performed a time-trend analysis of authorised products for conditions affecting children and adults (Figure 26).

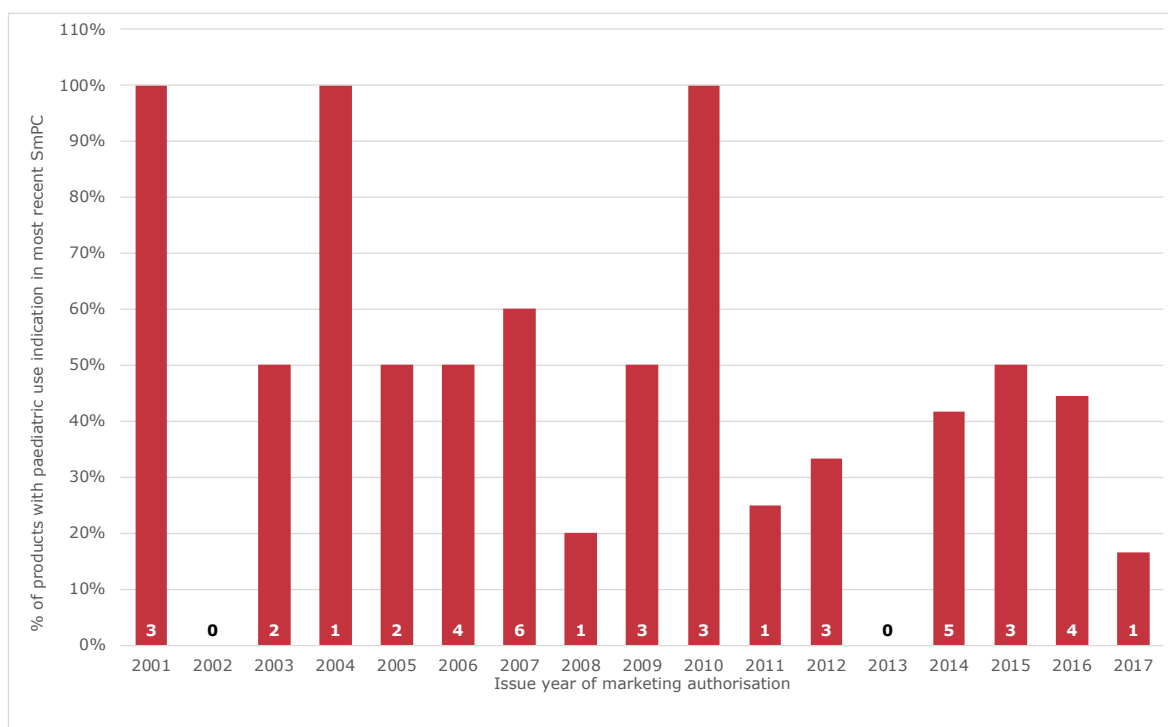
In half the years fewer than 5 such products were authorised, rendering the analysis susceptible to relatively large variations. Nonetheless, it is clear that a considerably lower share of the products authorised after 2010 have a paediatric use indication in their most recent SmPC than of products authorised in the first decade after introduction of the EU Orphan Regulation (34% versus 53%). This

⁶³ Only 4 therapeutic areas have 8 or more products authorised for conditions affecting both children and adults: Oncology (ATC code L, n=35), alimentary tract and metabolical conditions (ATC code A, n=21), blood and blood-forming disorders (ATC code B, n=9) and cardiovascular conditions (ATC code C, n=8).

⁶⁴ Here defined as all products with ATC code L, thus including all immunomodulating agents.

signals that indeed paediatric use indications are often added some time after the product is first authorised. However, the here presented analysis did not look into any underlying reasons for why paediatric use indications had not been added or what the status was of any paediatric investigations. It is worth also recalling that, prior to the introduction of the EU Paediatric Regulation in 2007, sponsors were not required to prepare (and conduct) a paediatric investigation plan.

Figure 26 Authorised orphan medicines with a paediatric use indication for conditions affecting adults and children by year of authorisation



Source: Data provided by EMA and information on paediatric use contained in the SmPC available in April 2019. The numbers at the base of the column display the number of marketing authorisations issued that year for orphan medicines for conditions affecting adults and children.

5.5. Types of marketing authorisation

The EMA records on what 'legal basis' products receive a marketing authorisation. The term 'legal basis' refers to the type of data that a sponsor has submitted in support of the application. The following categories are herein distinguished⁶⁵:

- **New active substance:** Data requirements fulfilled by applicant's own data, sometimes complemented with published literature data⁶⁶

⁶⁵ The categories have been selected and defined based on information provided by the EMA.

⁶⁶ In accordance with Article 8(3) of Directive No 2001/83/EC and Directive 65/65/EEC article 4.8(a).

- **Known active substance:** Data requirements fulfilled by applicant's own data, sometimes complemented with published literature data – no demonstration of new active substance⁶⁷
- **Hybrid application:** Applications of generics for which bioequivalence cannot be shown or which differ from the originator product in therapeutic indication, strength, pharmaceutical form, or route of administration⁶⁸
- **Well-established use:** Nonclinical and clinical data exclusively from literature. Sponsor's data required to establish comparability of product to product used in the literature⁶⁹

Across the total set of 142 authorised orphan medicines analysed, **the majority of application for orphan medicines were for new active substances (77%)**(Table 6). Applications on the basis of well-established use are least common and happened in the case of only six authorised orphan medicines (EMA data, 2018).

Table 6 Legal basis for authorisation of orphan medicines⁷⁰

Legal basis	Applications (%)
New active substance	109 (77%)
Known active substance	21 (15%)
Hybrid application	6 (4%)
Well-established use	6 (4%)
Total	142

Source: EMA, 2018.

5.6. Intellectual property rights and market exclusivity

As established in Section 3.2.1, **there are several types of intellectual property rights and regulatory protections from which a sponsor of an EU authorised orphan medicine can benefit.** Aside from the orphan market exclusivity, these include patents (e.g. on the active substance, formulation, indication or process), supplementary protection certificates (SPCs), data exclusivity and market protection. As explained previously, these differ in the

⁶⁷ Including complete stand-alone applications in accordance with Article 8.3 of Directive No 2001/83/EC, stand-alone applications in accordance with Directive 65/65/EEC a. 4.8 and bibliographical applications according to Article 10.1(a).

⁶⁸ In accordance with Article 10(3) of Directive No 2001/83/EC.

⁶⁹ In accordance with Article 10a of Directive No 2001/83/EC.

⁷⁰ Some of the products were submitted before the current legislation came into force. At that time, sponsors were not required to indicate whether the active substance was known or not. Moreover, before 2010, the CHMP was not actively assessing the claim of an active substance being new. Thus, for those products, the categorisation was based on the sponsor's claim only. For this study, the EMA has retroactively classified those products from prior to the current legislation. It indicates that for 5 authorised orphan medicines they made a best approximation of the status of the active substance at the time of authorisation.

term of protection they offer, as well as in the scope of the protection conferred onto the product.

To understand what value is offered by the market exclusivity, we have analysed in how far it extends the effective protection period for authorised orphan medicines (Table 7).⁷¹

Table 7 Overlap between major patent/SPC protections and orphan market exclusivity on authorised orphan medicines

Patent /SPC protection	Number	Percentage	Average additional protection by market exclusivity
No primary patent/SPC ⁷² at start of marketing exclusivity period	31	30%	10 years
Primary patent/SPC in force at start of first marketing exclusivity period	74	70%	
Primary patent/SPC still in force at end of (last) marketing exclusivity period	51	69%	none
Primary patent/SPC expired at end of (last) marketing exclusivity period	23	31%	2 years, 3 months

Source: MPA, 2018 (*Total number of orphan medicinal products in this analysis = 105; there are also orphan medicines without patent protection).

⁷¹ Our analysis has focused on protection by primary patents and SPCs. Data exclusivity and market protection have not been taken into consideration. These are triggered by the first marketing authorisation in the EU on a particular product for a maximum period of 11 years (following the '8+2+1' rule as explained in section 3.3.5). Therefore, these protections would almost never exceed the period of market exclusivity for a designated orphan medicine. The market protection offered under this rule is also weaker than the market exclusivity for orphan products for two reasons. First, the scope of protection for regular market protection is narrower (all 'similar' products for the orphan market exclusivity, compared to products chemically equivalent to the reference product for regular market protection). Second, market exclusivity for authorised orphan medicines precludes the EMA from even considering the dossier of a product similar to a protected orphan medicine for the full 10 years, whereas regular market protection prevents the EMA from issuing a marketing authorisation referencing the orphan medicine for the same 10 year period (11 in some cases) but does not bar it from already assessing the dossier after 8 years.

⁷² Either no primary patent or SPC could be identified, or this had expired prior to the start of the market exclusivity. On some of these products, it is possible that there are still patents or SPCs connected to methods or processes that were not considered in this analysis. For other products, the patents were still pending at the time of this analysis (Q3 2018).

Among 105⁷³ authorised orphan medicines analysed, **74 (70%) were protected by a primary⁷⁴ patent or an SPC at the time the market exclusivity went into effect** (Table 6). This indicates that the majority of newly authorised orphan medicines are new active substances that still benefit from substantial patent protection.

Of the 74 products protected by a primary patent or SPC at the start of the market exclusivity, **51 (69%) were still protected after the expiry of any market exclusivity⁷⁵, with an average duration of 3.5 years beyond the market exclusivity.**⁷⁶ For these products, the market exclusivity had no impact on prolonging the period of protection⁷⁷.

For the 23 products (31% of 74 products) for which the protection offered by a primary patent or SPC expired during the (first) market exclusivity period, **the average duration of the additional protection offered by market exclusivity was 2 years and 3 months.** For this set of products, the market exclusivity was the only remaining form of protection in the period after the patent/SPC ended, but this period was shorter than the 10 (or 12) years.

A little less than a third of analysed products was not protected by any primary patent or SPC at the start of the market exclusivity period. For this sub-set of products, the market exclusivity was the only remaining form of protection against competition throughout the entire 10 years duration (or 12 years, in the case of a paediatric extension to the exclusivity period). A third of the products without a major patent or SPC at the start of the market exclusivity is a biological, the other two-thirds are small molecules.

When averaged over the entire set of analysed orphan medicines, thus including products without any primary patent or SPC protection at the start of the market

⁷³ Not all tradenames of the 142 authorised orphan medicines could be definitively connected to the correct active substance on which a primary patent was filed in the patent information database that was used for this analysis. However, the sample of 105 appears sufficiently representative to allow for extrapolation of the findings to the larger dataset.

⁷⁴ For this analysis, only primary composition patents were considered. Further medical use patents, process patents or formulation patents were not taken into account. Whilst such 'secondary' patents do in fact delay generic entry as well, they are generally viewed as offering a 'weaker' protection and their impact on deterring generic entry thus is more limited.

⁷⁵ Our analysis accounts for the effect of multiple (partially) consecutive periods of market exclusivity in case a product has been authorised for more than one orphan condition. In interviews, sponsors have suggested that – due to the possibility for off-label use – enforcement of the market exclusivity for second and further orphan designations is challenged. As this claim could not be validated, we have interpreted the existence of *any* market exclusivity on the products, irrespective of the orphan indication, as conferring additional protection. As the number of products to which this situation applies is anyways limited, and the market exclusivity periods tend to be relatively close together, the effect of this assumption on the overall result is small.

⁷⁶ Calculation based on the time of expiry of the primary patent/SPC relative to the expiry of the (last) period of market exclusivity, and averaged over all 51 products for which the primary patent/SPC expired after any market exclusivity.

⁷⁷ However, as noted in other sections of this report as well, the market exclusivity still represented an additional layer of protection against similar products and as such cannot be said to have had no impact at all.

exclusivity period, **the average additional protection offered by the market exclusivity was calculated at 3.4 years.**⁷⁸

As indicated previously, under the EU Orphan Regulation a product can obtain multiple orphan designations if the product has multiple orphan indications (as opposed to therapeutic indications that fall within the same orphan indication). Each of these designations can trigger a new period of market exclusivity upon authorisation.

To understand how this can impact the effective protection conferred by the market exclusivity, we analysed how many orphan medicines have been authorised for more than one orphan indication.⁷⁹ Among authorised orphan medicines, the vast majority (122, 86%) have been authorised for just one orphan indication. In total, **20 products have been authorised for two or more orphan indications** (Table 8). The vast majority (n=15, 75%) of these are oncological treatments.

For **11 products, there was a time gap between marketing authorisations.** This meant that these products had **partially consecutive periods of market exclusivity** for different indications. This time gap was longest for the products Carbaglu and Revlimid where the last indication was authorised nine years after the first. For nine products, all market exclusivity periods ran concurrently.

Table 8 Orphan medicines authorised for multiple orphan indications

Product	# Authorised orphan indications	ATC code	Time between authorisation of first and last orphan indication (rounded to nearest year)
Glivec*	6	L	5 years
Nexavar	3	L	8 years
Revlimid	3	L	9 years
Carbaglu	2	A	9 years
Zavesca*	2	A	7 years
Soliris	2	L	5 years
Tracleer*	2	C	5 years
Signifor	2	H	3 years
Gazyvaro	2	L	2 years

⁷⁸ This estimate is based on the following summation: 31 products with the full 10 years of market exclusivity extending beyond any patent/SPC (=31x10), 51 products with market exclusivity fully within the period of patent/SPC protection (=51x0), 23 products with an average period of market exclusivity after expiry of patent/SPC of 2.25 years (=23x2.25). Divided over all 104 products, this gives an average duration of the market exclusivity beyond the primary patent/SPC of 3.4 years.

⁷⁹ The count of products authorised for more than one orphan indication could not be performed directly on the data set provided to the study team by the EMA. Discussions with the Orphan Office of the EMA were needed to clarify where designations had been 'bundled' under a single indication at the time of marketing authorisation. Whilst this list was confirmed by the EMA, it was noted that it may not be fully up-to-date.

Torisel*	2	L	2 years
Yondelis	2	L	2 years
Adcetris	2	L	All indications authorised on the same date
Cresemba	2	J	All indications authorised on the same date
Iclusig	2	L	All indications authorised on the same date
Imbruvica	2	L	All indications authorised on the same date
Lenvima*	2	L	All indications authorised on the same date
Rydapt	2	L	All indications authorised on the same date
Sprycel*	2	L	All indications authorised on the same date
Sutent*	2	L	All indications authorised on the same date
Vidaza*	2	L	All indications authorised on the same date

Source: EMA 2018. * no longer on the community register for orphan medicinal products

5.7. Characteristics of sponsors of orphan medicines

The objectives of the EU Orphan Regulation, presented previously in Section 3.2 (Figure 4), include encouraging innovation and providing incentives for industry to develop and market orphan medicines. As part of these objectives, the Regulation has aimed to attract a new set of players to the field and offers incentives that, although not exclusive to, are mostly aimed at smaller and less experienced product developers. To understand to what extent the Regulation has been able to attract such developers to the field, analyses were performed of all sponsors of orphan designated products and authorised orphan medicines.

Two separate sets of sponsors have been considered:

- **Initial sponsors:** those that applied for and were granted the orphan designation
- **Current sponsors:** those listed as sponsors as of 2017-Q4

A separate list of all transfers of designations was hereto provided. As the EMA data do not classify sponsors by type of organisations, categorisation was manually performed on the basis of publicly available information.

We have distinguished between different types of sponsor:

- **Pharma:** Pharmaceutical or biotechnology companies, that are *not listed* on the EMA SME register for small- and medium-sized enterprises
- **SME:** Pharmaceutical or biotechnology companies, that are *listed* on the EMA register of small or medium-sized enterprises
- **Research:** Organisations that are identifiable as academic institutions or independent research institutes (and that are not listed on the EMA SME register)
- **Individual:** These may be associated with academic institutions, but are listed as sponsors in their own right

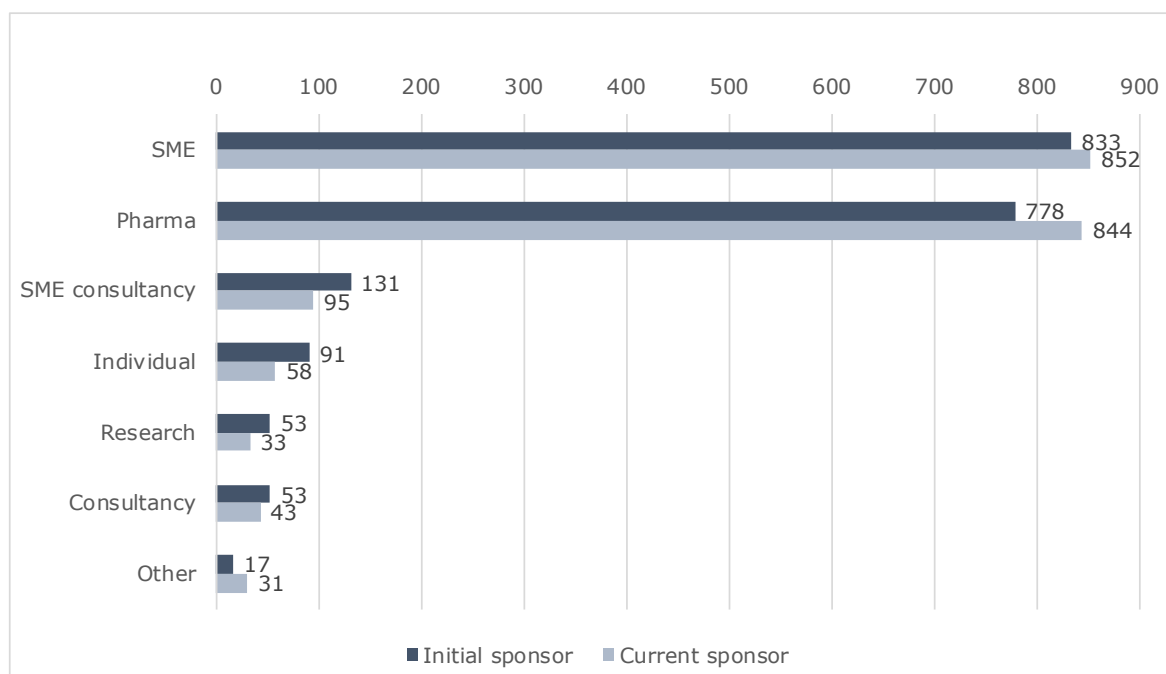
- **Consultancy:** Specialised consultancies, often with a focus on regulatory affairs. As many of these are also included on the EMA SME register, they are separated into:
 - SME consultancy
 - Consultancy
- **Other:** Entities that could not fit well into any of the other categories. These include, for instance, charitable foundations

Overall, there are **1,050 individual entities listed as initial sponsors, and 992 unique entities listed as current sponsors.**⁸⁰ There are **96 unique entities among marketing authorisation holders of authorised orphan medicines.**

SMEs and pharmaceutical companies are sponsors for a similar share of designations. Among initial designations they hold 43% and 40% respectively. For current designations (which includes all initial designations that have never (yet) been transferred), their respective shares are 44% and 43% (Figure 27

Figure 27 Initial and current sponsor by type of entity). Only 7% of all initial designations, and 5% of current designations is held by individuals or research institutions. A slightly larger role is played by regulatory consultancies, which are listed as sponsors for a little under 10% of all designations.

Figure 27 Initial and current sponsor by type of entity

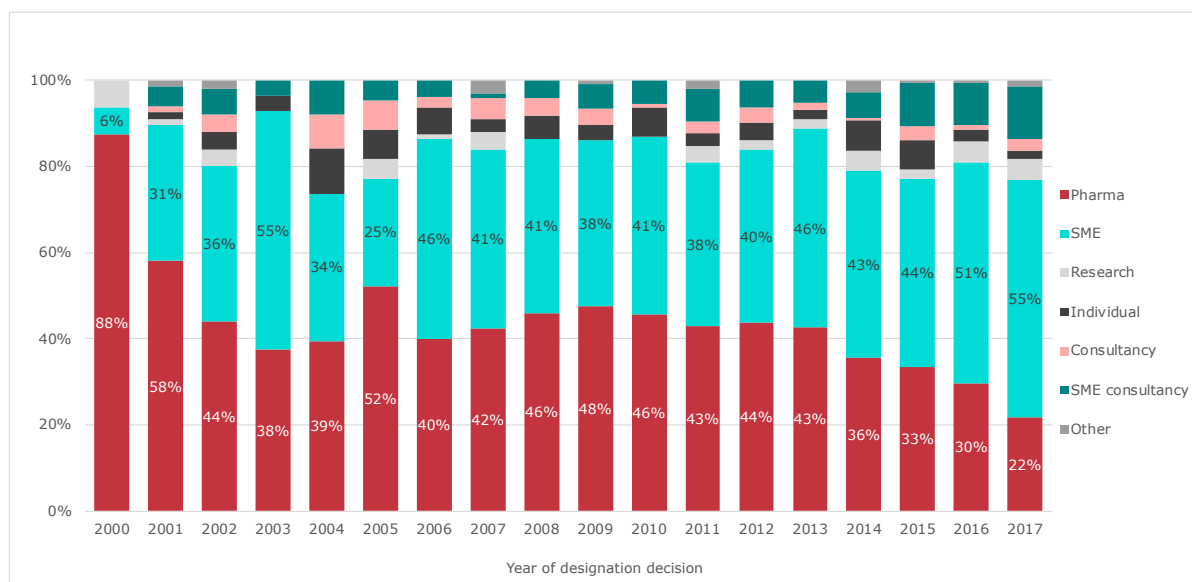


⁸⁰ This analysis is based on distinct entries in the sponsor name field. Whilst we have corrected for obvious spelling variations (e.g. Ltd versus Limited in the company name), names may in fact belong to the same entity but have not been recognised as such.

Source: EMA data, 2018 (2000-2017 Q4), classification by Technopolis Group

Remarkably, the share of designations granted to pharmaceutical companies in recent years has sharply declined, whilst the number of designations granted to SMEs has grown to over half of all designations (Figure 28).

Figure 28 Share of designations granted annually by type of sponsor



Source: EMA data, 2018 (2000-2017 Q4), classification by Technopolis Group

A study that compared the type of sponsors of orphan designated products across jurisdictions found that in Japan large pharmaceutical companies (among global top ten for revenue) accounted for 35% of applicants but for only 15% in the US and 10% in the EU (Murakami & Narukawa, 2016). Our own analysis did not attempt to further classify pharmaceutical companies among initial sponsors by revenue. The study, furthermore, found that 5% of designations in the US and 6% in the EU – in line with our own analysis – came from academia or other similar institutions, while there were none in Japan. This most likely reflects the fact that in Japan only products that are in late stage development, and for which there is a high probability that they will lead to a successful product, are eligible for designation.

A total of 640 designations (33%) have been transferred from one sponsor to another at least once.⁸¹ Transfers have happened most often between pharmaceutical companies (187 transfers) (Table 9). Overall, transfers trend from smaller to larger entities: from individuals or research institutes to SMEs (39 transfers), and from SMEs to (mostly larger) pharmaceutical companies (95

⁸¹ A transfer is defined as any change in registered sponsor. This includes transfers within a company, when a designation is moved from one subsidiary to another. It also includes a registration change when a company – so not only a product – is acquired by another company. Therefore many of the here included transfers are administrative changes rather than a true transition of ownership.

transfers). Transfers in the reverse direction are considerably rarer (5 and 57 transfers respectively).

Consultancies, both those on the SME register and those that are not listed, appear to play an intermediary role with the majority of transfers happening away from these entities (99 overall), rather than towards them (19 transfers).

Table 9 Transfer of designations between sponsors by type of entity

		Current sponsor						
Initial sponsor	Individual	Research	SME	Pharma	Consultancy	SME consultancy	Other	Total
Individual	2		31	12				45
Research		1	8	11		1		21
SME	4	1	95	95	4	10		209
Pharma	5		57	187	6	10		265
Consultancy			9	10	2	1		22
SME consultancy	1		28	29		8	11	77
Other							1	1
Total	12	2	228	344	12	30	12	640

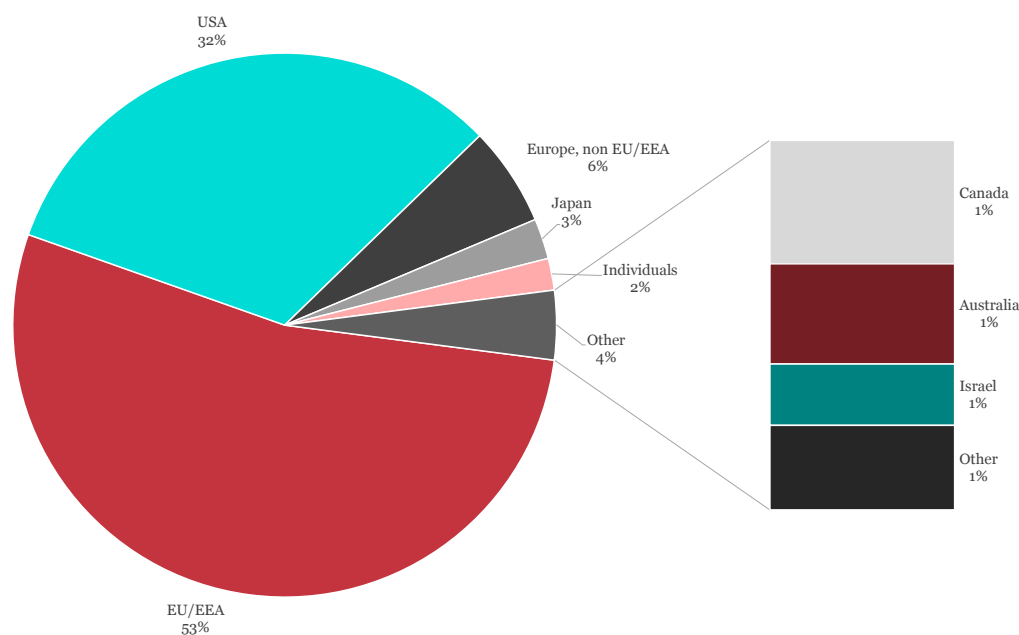
Source: EMA data, 2018 (2000-2017 Q4)

Whilst the EU Orphan Regulation contains no specific provisions that R&D should be conducted in the EU/EEA region, loss of competitiveness of the EU at international level and reduced investment in R&D were identified as some of the problems the Regulation sought to address (Section 3.3, Figure 4). Therefore, we explored where sponsors, both initial and current, originated. The EMA data on sponsors was hereto not usable, though, due to the Regulation's requirement that all sponsors are established in the EU/EEA. As a result of this requirement, all sponsors that are not headquartered here have used either an EU/EEA-based subsidiary, or a regulatory consultancy to act as intermediary. Instead, we therefore relied on publicly available company information to establish where headquarters are based.

Among current sponsors of orphan designated products, 53% are considered to be headquartered in the EU/EEA, and another 32% originate from the US (

Figure 29). Of marketing authorisation holders of orphan medicines, around 40% are headquartered in the EU.⁸²

Figure 29 Current sponsors by location of headquarters



Source: EMA, 2018.

To track how designations move between jurisdictions, we analysed all transfers from initial to current sponsor by location of the sponsor (Table 10). Around a quarter (28%) of designations initially held by a sponsor from the EU/EEA moves to a sponsor in a country outside the region, most often the US. A similar share (22%) moves in the opposite direction. The remainder of designations has neither transferred in, nor out of the EU/EEA region.

⁸² Assessment based on the location of the headquarters of the parent company at the end of 2017, thus not necessarily accounting for where headquarters were based at the time of marketing authorisation in case the company was taken over. A further 29 marketing authorisations belong to companies headquartered in Switzerland, which is not part of the EU/EEA region but part of the European single market.

Table 10 Transfers of designations by location of sponsor

Initial sponsor	Current sponsor	%
EU/EEA	EU/EEA	22%
EU/EEA	Non-EU/EEA	28%
Non-EU/EEA	EU/EEA	22%
Non-EU/EEA	Non-EU/EEA	27%

5.8. Availability of and access to authorised orphan medicines in the EU/EEA

The IQVIA-database (Appendix F) enables us to determine for the period 2008-2016 (full years) the total sales value⁸³ of individual orphan medicines that are available on the EEA market.⁸⁴ From the total group of identified orphan medicines, the database provides sales data for 105 orphan medicines, which were present in the market in this period.

For the total period and for all available orphan medicines, a total sales volume of €44.1b is recorded. Over this period, we observe that the annual sales increase significantly: from €2.4b in 2008 to €8.3b in 2016. This increase is related to two main factors: (1) more orphan medicines that received marketing authorisation and entered the market and (2) an increase in the number of Member States, which show 'sales' in the IQVIA-database.

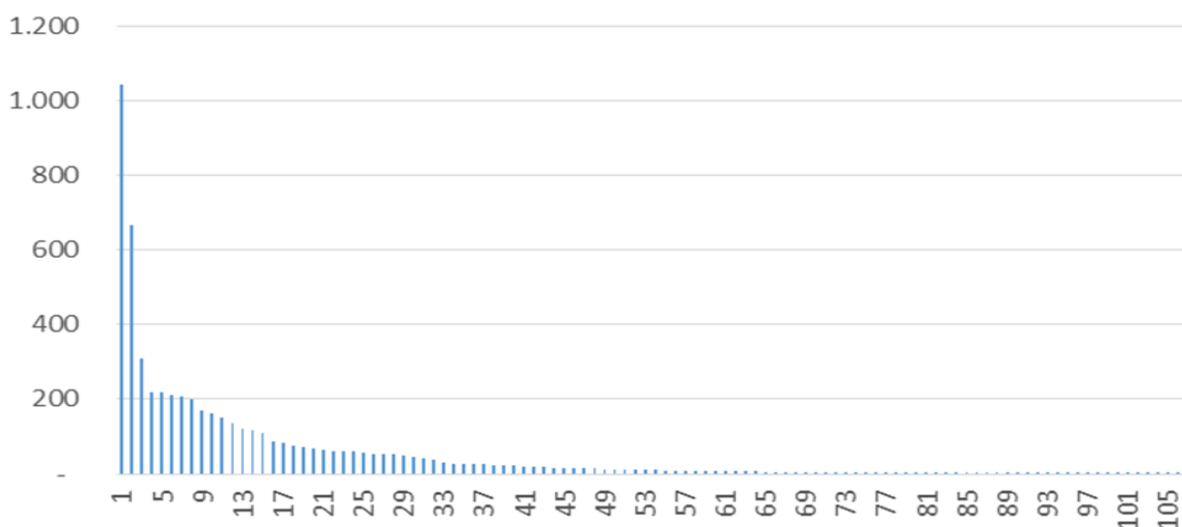
Within the whole group of identified orphan medicines, **we observe a large variation between the orphan medicines in terms of annual sales revenues** (Figure 30). Approximately 50% of the orphan medicines have an average annual sales revenue of €10m or less and approximately 15% of the orphan medicines show annual sales revenues of more than €100m. For the total group of 105 orphan medicines, the median⁸⁵ is €10m. Turnover realised by orphan medicines (with both active and expired market exclusivity) was on average €56m per annum during 2008-2017.

⁸³ The IQVIA-database reports revenue data on a quarterly basis, in principle these revenues are based on 'list prices'.

⁸⁴ This data represents only market data for the period 2008-2016 in the EEA; due to licence restrictions for the IQVIA-database, similar market data is not available for the period 2000-2007 or for non-EEA markets.

⁸⁵ The median represents the observation separating the first (higher) half from the second (lower) half of a data sample.

Figure 30 Average annual sales revenues orphan medicines (2008-2016, in € million)

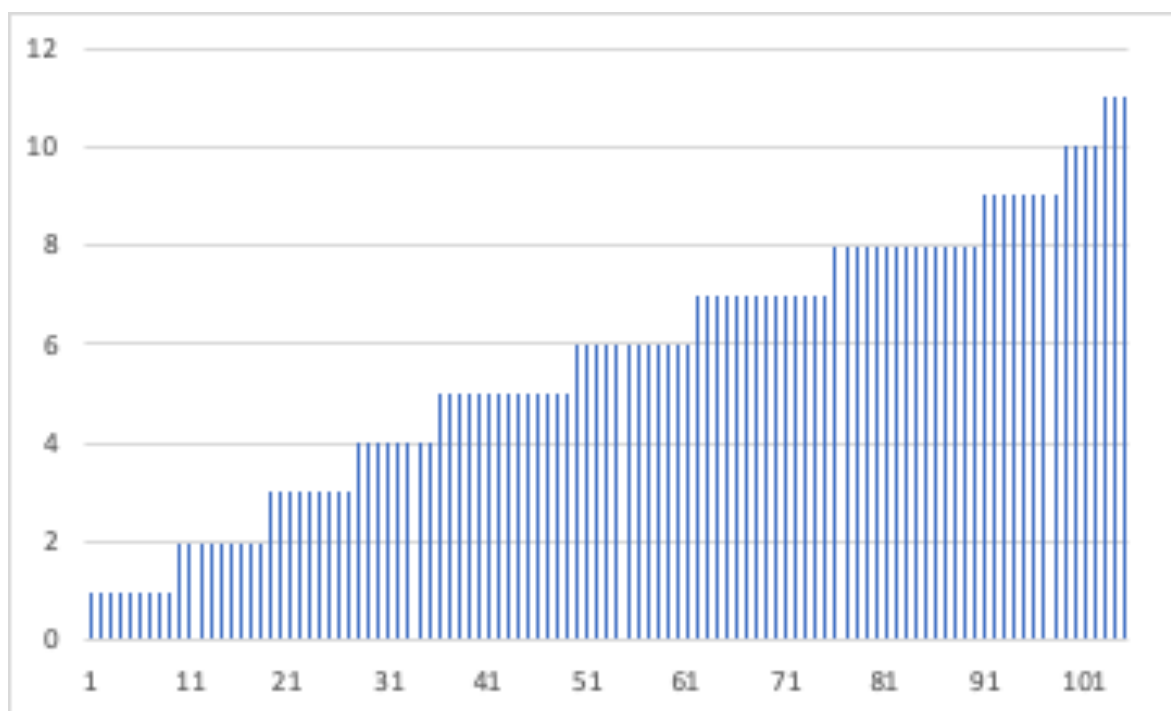


Source: IQVIA-data. Note: within the total group of identified orphan medicines, sales data were available for 105 orphan medicines.

Although orphan medicines may be available on the EU market, there are differences in speed with which they become accessible for patients in individual EU Member States. Further analysis of sales data shows that 88% of orphan medicines that received marketing authorisation became immediately available in at least one EU12-market⁸⁶. For the whole group, the average time to reach the first EU12-market was one month. In the first three years after marketing authorisation the orphan medicines reach, on average, 5.7 Member States from the EU-12. Figure 31 presents an overview of the number of EU-12 Member States an orphan medicine has reached in the first three years after EU marketing authorisation. The figure also shows that none of the orphan medicines reached all Member States with this period.

⁸⁶ The EU12 has been used as this represents a fixed group of countries throughout the period 1995-2017 enabling a comparison with orphan-like products.

Figure 31 Number of EU-12 Member States reached by an orphan medicine in the first three years after EU marketing authorisation



Source: IQVIA database.

5.9. Support for research on rare diseases

As part of the set of incentives, the EU Orphan Regulation also introduced the incentive 'aid for research' (Section 3.3.5). Effectively, this means that Member States or the European Commission can use the orphan designation as a condition to be considered for research funding.⁸⁷

At the level of the European Union, there are various programmes that support, among other things, rare disease research and the development of orphan medicines. These are discussed in more detail in section 5.9.1. In addition to these European programmes and initiatives, section 5.9.2 outlines some of the initiatives taken at Member State level to support patient care and research for rare diseases. Although the data presented in these two sections give some insight into the level of activity and funding, it is not possible from this to estimate the overall research funding for rare diseases in the EU with any degree of certainty. In part, this is because, whilst some research programmes or projects are very clearly aimed at understanding rare diseases or at developing treatments for these, others may be much more fundamental in nature. Even if research is not specifically aimed at rare diseases, the outcomes may have the potential to support also development of orphan medicines. Additionally, although some national funders may also open specific calls for rare disease research, this type of research may equally be funded through more open calls. Unless the funder explicitly categorises such research project as 'rare diseases

⁸⁷ For more information see: <https://publications.europa.eu/en/publication-detail/-/publication/c2ba4fd4-ae31-11e7-837e-01aa75ed71a1/language-en/format-PDF/source-69927191>

focused' they may not be recognised as such. Last, the CORDIS database contains information on EU funded research project but there is no single, connected database that contains information from national funders in the Member States. In fact, national funders do not usually have publicly accessible and searchable research funding databases that would enable rare disease related projects to be identified.

Despite these limitations, what these European and national programmes together demonstrate is that, overall, in the 18 years since the introduction of the EU Orphan Regulation, there has been a clear increase in research-related accompanying measures, and specifically in the:

- Level of public funding available for rare disease research, at the EU and national levels
- Level of coordination of national and international research agendas in rare diseases
- Extent of the data and knowledge infrastructure for rare diseases, from patient registries to biobanks

5.9.1. EU research and innovation actions

At the European level, a number of programmes and initiatives have supported research for rare diseases. The main identified programmes and initiatives are:

- The EU Framework Programmes for research and technological development, in particular the seventh EU Framework Programme (FP7) and its successor, Horizon 2020, including the ERA-Net research programmes on rare disease research E-Rare
- The International Rare Diseases Research Consortium (IRDiRC)
- RD-ACTION
- European Reference Networks (ERNs)

The following paragraphs discuss each of these in more detail.

The EU RTD Framework Programmes for research and technological development

As noted in Section 2.4, the EU's support for rare disease research was initiated within the fourth EU RTD Framework Programme (FP4) and confirmed and expanded within the fifth Framework Programme (FP5), with the number of supported projects increasing from 23 within FP4 to 47 within FP5.

In the intervening period and following the implementation of the EU Orphan Regulation in 2000, the EU reconfirmed its commitment to rare disease research with a larger programme of work within each successive EU RTD Framework Programme.

The seventh Framework Programme⁸⁸ for research, technological development and demonstration activities (2007-2013) (FP7) supported 120 rare disease projects under the *Health* theme. Support was available for projects that shed

⁸⁸ https://ec.europa.eu/research/fp7/index_en.cfm?pg=health

light on the course and/or mechanisms of rare diseases, or test diagnostic, preventive or therapeutic approaches.⁸⁹

Horizon 2020⁹⁰ has continued the EU's commitment to funding rare disease research and upon its completion will likely have more than doubled the investment made under FP7.

In a 2017 publication, the European Commission indicated that, at the time, 164 research projects into rare diseases had been supported by FP7 and H2020, with a total value of €874m. In addition to that, private research organisations in this field were supported with €180m. (The European Commission, 2017). Horizon 2020 and FP7 combined have committed more than €1b to collaborative rare disease research over the last ten years or so (European Commission, 2018).

ERA-Net research programmes on rare diseases (E-Rare)

The **ERA-Net research programmes on rare disease research, E-Rare**⁹¹ are a good example of the evolution in support for rare disease research in the 18 years following the implementation of the EU Orphan Regulation.

E-Rare was implemented first in 2006, in the closing stages of the sixth EU Framework Programme (FP6) with the aim of fostering an increased focus on rare disease research at the level of individual EU member states.⁹² The pooled national funds were matched by EC funds and were used to support various coordination activities (e.g. setting of a common research agenda) and to fund transnational research to complement the bigger multinational groups funded by the EU.

The initial partnership, **E-Rare 1**, consisted of eight countries who issued two transnational calls in 2007 and 2009. The Commission approved a follow-on project under FP7, E-Rare 2, which ran from 2010-2014. **E-Rare 2** had an expanded network, with the original eight EU member states increasing to 15 countries and with annual calls for proposals. In addition to an increase in the number of research projects supported, the network also redoubled its efforts to enhance coordination among member states by enabling information exchange and extension of the rare disease research funders network.

The network earlier success led to a further proposal within Horizon 2020 and the launch of **E-Rare 3**, again with a larger membership and an expanded agenda. E-Rare 3 is made up of 26 public bodies, ministries and research

⁸⁹ European Commission (2016), Working document: Ex-Post Evaluation of the Seventh Framework Programme, January 2016.

⁹⁰ http://ec.europa.eu/research/participants/data/ref/h2020/wp/2018-2020/main/h2020-wp1820-health_en.pdf

⁹¹ <http://www.erare.eu>.

⁹² The ERA-NET instrument is a generic instrument that provides EC financial support to Member State level 'public-public' partnerships (typically amongst research funders) in the preparation and implementation of joint research actions of a transnational nature.

funding organisations from 18 countries⁹³ (Julkowska et al., 2017). Since its inception, E-Rare has launched eight Joint Transnational Calls (JTCs) for projects, with a total investment value of €92m.

The E-Rare network has established good links with the international rare diseases research community and its programme of work follows the basic guidelines defined by the **International Rare Disease Research Consortium (IRDiRC)** (see next Section)(Hedley, Murray, Rodwell, & Aymé, 2016).

International Rare Disease Research Consortium (IRDiRC)

Another important initiative is the **International Rare Disease Research Consortium (IRDiRC)**⁹⁴, established in 2011. The idea was conceived by the European Commission, via the Directorate General for Research and Innovation (DG RTD), and the US National Institutes of Health (NIH). Its purpose was to expedite progress in rare disease research by coordinating rare disease research funding (Julkowska et al., 2017). Funding of the IRDiRC is provided by its members, including several EU28 countries, Australia, Canada, China, South Korea and the United States. The exact investments are unknown. (Aymé S, 2013)

The IRDiRC recognises that coordinating efforts to overcome common barriers in the development of orphan medicines is key to maximising the impact of collective global investments. To navigate this difficult area, it has developed a set of policies and guidelines to be followed by its members, in areas such as data sharing and standards, patient registries and intellectual property (Lochmüller et al., 2017).

The consortium endeavours to highlight the most important areas requiring support within rare disease research and the benefits of data sharing and collaboration while also encouraging the involvement of patients as main actors and stakeholders within the research process (Julkowska et al., 2017).

The European Commission supports IRDiRCs objectives by funding the logistical organisations of its activities (C. Rodwell & Aymé, 2014).

RD-ACTION

The RD-ACTION⁹⁵ (2015-2018) project was set up to meet diverse challenges of rare diseases at EU level: it must expand and consolidate the achievements of two previous Joint Actions on Rare Diseases supported by the European Commission: the Joint Action Orphanet and the European Union Committee of Experts on Rare Diseases⁹⁶ (EUCERD) Joint Action.

⁹³ Austria, Belgium, France, Germany, Greece, Hungary, Italy, Latvia, Poland, Portugal, Romania, Spain, the Netherlands, Switzerland, Israel, Turkey, Canada and Japan.

⁹⁴ <http://www.irdirc.org/>

⁹⁵ <http://www.rd-action.eu/>

⁹⁶ The mandate of the EUCERD expired in 2014. The EUCERD has been succeeded by the European Commission Expert Group on Rare Diseases.

European Reference Networks

Another important European initiative to support both patient care and research on rare diseases is the creation of European Reference Networks (ERNs).⁹⁷ The ERNs serve as information, research and knowledge centres with the aim of contributing to the most recent scientific findings. Furthermore, they should facilitate the management of patients from other EU countries when no in-country expert is available and ensure availability of subsequent laboratory and treatment facilities when required (Parker, 2014). Research is a key element of the ERNs, providing an integrated structure to facilitate collaboration and creating a knowledge hub to encourage translational research and the creation of cross-border registries (Julkowska et al., 2017). In March 2017, the first 24 ERNs were launched.⁹⁷ The patient federation EURORDIS has expressed a desire that all rare disease patients are covered by a minimum of one ERN (EURORDIS, 2011).

EU contributions to rare disease research

The here listed initiatives underscore that, alongside the incentives offered by the EU Orphan Regulation, the EC has invested considerably in research for rare disease in other ways. This includes support for basic research, such as what is supported through the EU framework programmes and support for the creation of an infrastructure to promote knowledge sharing. Estimates of the financial contributions have been summarised in Table 11.

Table 11 EC funding contributions to rare disease research

Initiative	EC contribution to rare disease research
Seventh Framework Programme for Research and Innovation (FP7)	€624m (based on non-public data provided by DG SANTE from the Cordis database)
Horizon 2020 and ERA-NETs (E-Rare 1, 2 and 3)	Contribution of €120-125m by the EC (€5m to E-Rare 1 and E-Rare2, €60m for new therapies for rare diseases, €5m for integration and opening research infrastructures and €50-55m for the Rare Disease European Joint Programme Cofund) In E-Rare 1 (2006-2010), and E-Rare 2 (2010-2014) overall €56.4m was invested. (Aymé S, 2013) In E-rare 3 (2015-2019), more than €90m was invested. (European Commission, 2017b)
International Rare Diseases Research Consortium (IRDiRC)	€95m (through the call FP7-HEALTH-2012-INNOVATION-1)
RD-ACTION ('joint action' on rare diseases)	€8.3m. (Hedley et al., 2016).
European Reference Networks	The ERNs are supported from several EU funding programmes, including the Health Programme, the Connecting Europe Facility and Horizon 2020.

5.9.2. National research activities

At the level of the EU Member States, various 'other incentives' have been put in place to complement the EU Orphan Regulation and further support the

⁹⁷ https://ec.europa.eu/health/ern_en

development of orphan medicinal products. A prominent place herein is taken by **national rare disease plans**. Such national rare disease plans are “aimed at guiding and structuring relevant actions in the field of rare diseases within the framework of their health and social systems.”(The Council of the European Union, 2009a) They commonly include a commitment to research funding.

Appendix G provides an overview of these plans and identifies the amount of funding committed under each. They cover a number of important aspects, including the mapping of medical expertise on rare diseases and better integration of European legislation with national healthcare and social systems. It is, however, not known to what extent commitments have been converted into actual spending on research for rare diseases and development of orphan medicines.⁹⁸ There is also a call to support innovative research at the national level and to champion participation in European and international research on rare diseases.

The research and coordination aspects of the national plans analysed reveal a reasonably consistent picture. As shown also in section 10.5.2, a majority of member states have (or had) a national programme for rare disease research. In most cases, there are specific rare disease programmes. In a minority of cases, support is available through a broader medical research programme where rare disease research proposals will have to win grant funding in competition with proposals from other fields.

The plans do not always disclose the available budgets. However, in the 15 cases where we have identified funding levels, it is clear **there are marked differences in the scale of activity**. Unsurprisingly, the larger Member States are spending more than smaller Member States; France, Germany and the UK are particularly active, allocating €25m-€50m a year in funding for rare disease research. The other EU Member States for which data were available are investing hundreds of thousands, rather than millions.

While we could not arrive at a definitive estimate of the total national investment in rare disease research relating to orphan medicines, **across all 28 EU Member States, these partial data suggest it is on the order of €200m a year currently**. That is broadly similar to the current level of earmarked investment through the EU research and innovation framework programme, albeit there is likely to be some element of double counting with national budgets being used for example to match fund EU actions. This rudimentary analysis does, however, suggest the EU Orphan Regulation has provided the catalyst to an expansion of activity at the level of member states, a subject to which we return in the evaluative chapters that follow.

5.10. Scientific developments

In the years since the EU Orphan Regulation went into effect, there have been a number of scientific developments that are having an important effect on the development of new medicines for rare diseases. Section 5.4.4 showed the evolution in the basis of new orphan designations, with **a growing proportion of all orphan applications being based on new technologies** (biologicals

⁹⁸ Publications on existing programmes and their impact do not always make a distinction between (fundamental) research in the field of rare disease and the development of orphan medicines

and advanced therapies) and a smaller proportion being based on more conventional 'small molecule' pharmaceutical compounds.

There have also been important developments over the past 20 years in the development of personalised medicine⁹⁹ whereby treatments are increasingly designed specifically for small subsets of patients. In parallel, the pressure to come forward with more innovative medicines earlier has led to important developments in the design of clinical trials. In both cases, these trends have provided an important backdrop to the evolution in the guidelines and practices relating to the functioning of the EU Orphan Regulation. In section 6.3 it is discussed how these developments affect the application of the regulatory framework for orphan medicines in the EU.

Personalised medicine and biomarkers

Advances in data analytics have catalysed the advancement of 'personalised medicine'. The premise of personalised medicine is based on the fact that 30% of medicines investigated in clinical trials fail because of lack of efficacy (Kola & Landis, 2004). **Stratifying patients and diseases based on molecular subtypes, then subsequently treating patients based on this subtype, can improve treatment efficacy.** Within the context of rare diseases, personalised genomic approaches are particularly relevant, as it is estimated that 80% of rare diseases have a genetic component (Thompson et al., 2014). Therefore emphasis has been placed on the therapeutic potential offered by the rapidly expanding fields of genomics, transcriptomics, metabolomics and proteomics in rare disease research (Aymé & Rodwell, 2013).¹⁰⁰ These technologies offer novel routes to identify new diseases, delineate biomarkers and identify new therapeutic targets. The Health Research Theme of the 7th Framework Programme gave a specific focus to rare diseases as models for personalised medicine with the application of 'omics to groups of rare diseases (Draghia-Akli, 2012)

As the understanding of the role of genes in specific diseases improves, and the costs for genetic testing decrease, **it is expected that personalised medicine will become increasingly widespread and within the next 20 years could be at the forefront of clinical applications** (Gülbakan et al., 2016).

A 2017 study by Kesselheim et al. investigated the use of biomarkers to define orphan sub-sets of more common diseases among US authorised orphan medicines (Kesselheim, Treasure, & Joffe, 2017). It found that, in the period

⁹⁹ "The Horizon 2020 Advisory Group has defined personalised medicine as "a medical model using characterization of individuals' phenotypes and genotypes (e.g. molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention". This definition was also used by EU Health Ministers in their Council conclusions on personalised medicine for patients, published in December 2015." (<https://ec.europa.eu/research/health/index.cfm?pg=policy&policynome=personalised>). For this report, a somewhat narrower interpretation was used, focused on identifying subsets of patients within a treatment population based on their genotypic information.

¹⁰⁰ The Health Research Theme of FP7 gave a specific focus to rare diseases as models for personalised medicine with the application of 'omics to groups of rare diseases (Draghia-Akli, 2012).

from 2009 to 2015, 13 out of 84 (16%) orphan medicines were for biomarker-derived subsets of more prevalent diseases, of which 11 addressed oncology indications. The authors note also that of the 39 oncology medicines that received an orphan designation in that period, 11 (28%) were for biomarker-derived disease subsets.

Novel trial designs

Specific challenges exist when undertaking clinical trials for rare diseases due to the small patient populations involved. These challenges can be made more acute by the tendency to relax well established standards for the evaluation of treatment efficacy, in order to get treatments to the patient faster (Hilgers, Koenig, Molenberghs, & Senn, 2016). Many rare diseases are heterogeneous, and therefore it can be difficult to obtain a clinically relevant population sample to study for a specific medicine. Additionally, it can be challenging to define good clinical parameters due to poor disease characterisation. A lack of understanding of the natural history of many rare diseases, can also complicate the estimation of an expected effect size and determination of an appropriate study duration (Hall & Ludington 2013).

The challenges of conducting adequately powered randomised trials in the field of rare diseases is underscored by the observation that, between 2000 and 2010, of the 63 orphan medicines that received a positive opinion from the EMA and received a European marketing authorisation, only 38 completed a randomised clinical trial (Joppi, Bertele', & Garattini, 2013). One third were examined in trials involving a sample of less than 100 patients, and 43% of the approved medicines had clinical trials lasting less than one year. These data suggest that studies relating to rare diseases are particularly vulnerable to bias, and it is difficult to complete an adequately powered trial to obtain a definitive treatment effect (Baldovino, Moliner, Taruscio, Daina, & Roccatello, 2016).

Novel clinical trial methods and adaptations of the traditional randomised controlled trial methodology for studying interventions in rare diseases have been proposed to accelerate access to safe and effective therapies. (Gagne, Thompson, O'Keefe, & Kesselheim, 2014). Some have focused on designs that allow for minimisation of sample size. Particular attention has herein focused herein on so-called **adaptive trial designs** which allow for modification of an aspect of the trial following a prospectively planned interim data analysis (Gagne et al., 2014).

Other novel trial designs have focused more on maximising the number of on-treatment patients. The possibility of being randomised into a non-treatment group can stop patients from enrolling in a clinical study, particularly when this would require them to abstain from other treatment options or when they have an opportunity to access experimental products. Patient recruitment to rare disease trials can thus be improved when participants can be guaranteed receiving an intervention.

One way to achieve this is through **cross-over trials**. These trials randomise patients to treatment or no treatment, like regular trial designs, but then switch at a certain point within the trial. From then on, the group previously receiving no treatment receives treatment and vice versa. This design is suited to studying (rare) chronic conditions in which treatments provide immediate relief of symptoms but where disease progression over time is slow (Gagne et al., 2014).

Basket trials enroll patients with multiple diseases and test more than one drug target in separate groups/cohorts within the same trial, making it possible to identify a potential response to targeted therapy with a relatively small

number of patients (Menis, Hasan, & Besse, 2014). This clinical trial approach may streamline and expedite the development of new treatments for rare diseases (Derhaschnig et al., 2016).

6. Relevance

The EU Better Regulation guidelines for evaluation define **relevance** as follows:

Relevance

Relevance looks at the relationship between the needs and problems in society and the objectives of the intervention and hence touches on aspects of design. Relevance analysis also requires a consideration of how the objectives of an EU intervention (legislative or spending measure) correspond to wider EU policy goals and priorities. Analysis should identify if there is any mismatch between the objectives of the intervention and the (current) needs or problems.

Source: Better Regulation Toolbox, #Tool 47.

An assessment of whether the EU Orphan Regulation has been a relevant instrument thus entails a review of the validity of the problem identification and of the objectives developed in response to these. The problems identified in the intervention logic presented in section 3.2 (Figure 4) could be summarised as a lack of treatments for patients with rare diseases in the EU and a market failure to develop such treatments, as well as insufficient and inequitable access to available treatments across the EU Member States.

This chapter focuses on the following evaluation questions:

- To what extent have the specific objectives underlying the adoption of the Orphan Regulation proven to be appropriate for addressing the problems? To what extent is the current scope of application of the Regulation catering for real (unmet) needs of patients? To what extent has, the Orphan Regulation addressed the issue of return on investment?
- To what extent are the provisions still an appropriate means for addressing one of the Regulation's main objectives, namely that patients suffering from rare diseases have access to the same quality of medicinal products as other patients within the EU? To what extent has this access been achieved across EU Member States and, if there are differences, what are the reasons for this?
- Which developments in the sector (e.g. advanced therapies, personalised medicine, scientific developments, use of real-world data, sustainability of national health care systems) have significant implications for the Regulation's relevance and future?

To address these questions, this chapter has been divided into three main sections. Section 6.1 deals with the issue of market failure to develop treatments for patients with rare diseases, examining the root causes of this market failure and the actions developed in response. It thus focuses on the specific objective of restoring equilibrium between supply and demand (see intervention logic as shown in Figure 4).

Section 6.2 revolves around the issue of availability of and access to orphan medicines for patients with rare diseases. These subjects relate to the specific objective of ensuring the same quality of treatment to patients with rare

diseases. An examination is performed of to what extent conditions have changed such that the relevance of the Regulation could be affected.

Section 6.3 focuses on the scientific and sectoral developments and how these have impacted the relevance of the Regulation or will have the potential for doing so in future.

6.1. Market failure to develop treatments for rare diseases

One of the main premises behind the EU Orphan Regulation was the observation that patients with rare diseases in the EU did not have the same level of access to good quality treatments as other patients.¹⁰¹ To assess the relevance of the EU Orphan Regulation it is thus necessary to understand *why* this problem existed: were treatments not being developed, did they exist but not reach patients sufficiently, or was there a combination of both these elements?

Section 2.2 already showed that, at the time the EU Orphan Regulation was introduced, indeed not only few treatments for rare diseases existed but that also availability of and access to any existing treatments was highly uneven across the European region. It thus appears there were problems in both the R&D ecosystem and in health systems across the EU.

This section focuses on the causes of failure to develop orphan medicines, and how the Regulation has sought to address these. It herein draws upon our own economic analyses, peer-reviewed literature and interviews and surveys with key stakeholders. The discussion on factors subsequently influencing availability of and access to developed orphan medicines is provided in Section 6.2.

The following paragraphs respectively touch upon the extent to which:

- Market failure to develop orphan medicines could be ascribed to insufficient economic incentives for industry to engage in R&D for development of orphan medicines, in particular the assumption that turnover for these medicines is low and does not provide sufficient basis for covering the costs of development. (Section 6.1.1)
- The instruments included in the Regulation were suited to dealing with the identified problems and causes (Section 6.1.2)
- This problem identification and proposed solutions remain valid under today's market conditions (Section 6.1.3)

6.1.1. Causes of market failures

In Section 2.2 it was described how, prior to the introduction of the EU Orphan Regulation, there were few medicines available for rare disease patients in Europe. A main reason for this was deemed to be that the market for medicines addressing rare diseases is small and subsequently R&D costs for orphan medicines could not be recovered from sales revenues, leading to market failures. The market exclusivity reward in particular was designed with this root cause in mind.

¹⁰¹ It should be kept in mind that access to medicines is a responsibility of the Member States and dependent on strategic decision-making by pharmaceutical companies. As such, the EC does not have direct influence on access to orphan medicines.

To determine whether this problem identification was correct, we have tested two main hypotheses:

- Orphan medicines are associated with low returns on investment more often than non-orphan medicines
- The expected low return on investment is a key barrier to development of orphan medicines

In the following sections, these respective hypotheses were tested using available literature, our own comparison of the turnovers for orphan and non-orphan medicines, and a targeted consultation of stakeholders, including product developers. However, the data collected does not always clearly allow us to distinguish between the conditions as they exist today and those that dominated the market at the time the Regulation was introduced. Therefore, these situations are discussed side-by-side, highlighting wherever possible what evolutions have taken place (further discussed in Section 6.1.3). This section also explores what other causes for the failure to develop orphan medicines existed and how this was taken into account in the Regulation's design.

Insufficient potential for return on investment

To test whether there is evidence that markets for orphan medicines are inherently less profitable than those for non-orphan medicines, we carried out an analysis of turnover of products in the EU/EEA, based on sales data. Parts 1 and 2 of Appendix F describe the steps taken to perform these analyses.

Table 12 gives the distribution of turnover for three groups of medicines. It shows that in **a large number of the cases turnover levels for orphan medicines are below €100 million per year**, with the majority of medicines showing turnover below €50 million. **There is, however, quite some variation** with some products showing annual turnover well in excess of €100 million. Turnover levels for orphan medicines that were introduced before 2000 (the 'orphan-likes') are not substantially different from those of orphan medicines introduced after 2000.

Table 12 Distribution of average annual turnover (2008-2016) for various types of products in the EU, by turnover class (million euro 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: own analysis of IQVIA database

A similar analysis for non-orphan products introduced after 2000 reveals that also here turnover levels can be low. At the same time, a larger share of non-orphan medicines shows higher turnover levels. The average annual turnover

level of these newly introduced non-orphan medicines is €83 million, which is almost 50% higher than for orphan medicines. These results for non-orphan medicines should be interpreted with some caution, though, as this group may include failed introductions and thus have a downward bias. This implies that the actual difference in average turnover may be more than 50%.

These results alone do not invalidate the hypothesis that low expected returns on investment in the absence of additional incentives were key reasons for the lack of treatment options for patients with rare diseases at the time the Regulation was introduced. Several caveats should be considered. First, our comparative analysis of turnover is based on market conditions as they exist *today* whereas there are **clear indications that the current market is a very different one from that at the beginning of the century** (Section 6.1.3).

Second, whilst some orphan medicines have proven to be highly lucrative (triggering the emergence of the term 'niche busters') (Kumar Kakkar & Dahiya, 2014), this does not negate the fact that our analysis shows **very small markets for some orphan products with turnovers of less than €10m per year**, in particular in the first years after introduction. Such a level is potentially insufficient to recoup the cost of investment. For these products in particular, the presence of economic incentives can make the difference between a decision to pursue or drop product development.

A final caveat to the analysis is that, whilst there is an obvious relationship between turnover (based on price and sales volume) and profit, the exact point at which a product becomes 'profitable' could not be accounted for in this analysis as the development costs are unknown. Therefore, it is **possible that even products with a high turnover are not (yet) being sold with a positive return on investment**. Conversely, products with a low turnover may still be sold with a positive return on investment, in case development costs were low. This issue of return on investment was explored in a 2008 study by Rzakhanov (Rzakhanov, 2008). It found that the return on investment for an orphan medicine exceeds that of non-orphan medicines four times (8.4% and 2.3% respectively). The difference was even greater when the orphan medicines are brought to the market (30.1% and 17.1% for orphan and non-orphan drugs, respectively).

We conclude that indeed **orphan medicines are more commonly associated with low turn-overs than other medicines, but the difference may be smaller than expected** at the time the Regulation was initiated. Whether this means that the return on investment for orphan medicines is 'insufficient' depends on the specific situation, taking into account development costs and generic competition.

As discussed in Section 3.3.1, the EU Orphan Regulation explicitly offers sponsors the possibility to request and obtain an orphan designation if a product is "intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community and that *without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment*". One might expect that, if expectation of insufficient return on investment is a such an important barrier to the development of orphan medicines, sponsors would regularly make use of this criterion to request an

orphan designation. However, to date, **only one application has been received on this ground** and this was subsequently withdrawn. Rather, all granted applications have been on the basis of the prevalence criterion.

In interviews, representatives from industry and the EMA have pointed out that it would in fact be challenging to designate products based on the 'insufficient return on investment' criterion. This is because **establishing return on investment, particularly at an early stage of development, requires an applicant to a priori estimate the future investments it will need to do. It would also need to estimate the returns on that investment before it is clear for what therapeutic indications the product may be used or at what price the product will be sold.** In addition, there is a potential cost of failure which also feeds into the expected returns on investment. The EMA, as a scientific assessment body, confirmed that it would be challenged to validate such economic estimates even though it will be required to do so in case an application on this ground would be made. Therefore, whenever a sponsor considers itself eligible for designation on the grounds of prevalence, it is far more likely to apply for designation on this basis.

Some stakeholders from outside of industry have suggested that the **lack of applications on the grounds of expectation of insufficient return on investment** is also because it could make **sponsors of economically successful products vulnerable to a reassessment under Article 8.2 of the Regulation** (The European Parliament and Council, 1999). Such a reassessment could lead to the market exclusivity period being reduced to six years, if the product is found to be sufficiently profitable. However, in interviews and surveys, sponsors did not offer this explanation.

One could reasonably argue that, by nature, products that are eligible for orphan designation on the basis of low prevalence of the targeted condition are less likely to generate sufficient returns on investment and that there is a strong correlation between the two criteria. Also, eligibility on the basis of prevalence is easier to demonstrate than expected low return on investment for the aforementioned reasons.

Nonetheless, the observation raises the **question of whether orphan designations are currently not also granted to products for which one could reasonably anticipate high returns on investment, simply because they meet the prevalence criterion.** Numerous stakeholders involved in this study have expressed the belief that this is in fact the case and that it runs counter to the intent of the Regulation.

Barriers to development of orphan medicines

Whereas the above analysis suggests economic reasons as an important barrier to development of orphan medicines, other barriers may play a role as well. These were explored through interviews and surveys with stakeholders, in particular developers. These were asked to identify what they consider to be the **biggest barriers to development of orphan medicines.**¹⁰²

¹⁰² The question focused primarily on what sponsors consider to be barriers presently, rather than what they viewed as the main barriers at the time of introduction of the Regulation. Nonetheless,

Most survey respondents (24 of 39) indicated that this relates to **a combination of scientific, financing and regulatory barriers**. Over 51% (20 of 39) stated that scientific barriers, such as insufficient knowledge on the causes of disease, pose the largest difficulty. They attributed this to difficulties in finding patients with rare diseases and recruiting these into trials. Also, unclear history of diseases, ethical issues and a lack of statistically significant results for a small population of patients complicate the research. The fact that many rare diseases comprise heterogeneous populations adds another layer of complexity for clinical trials, leading to questioning of methodologies and quality of findings.

Expectations of low return on investment were cited by 18 out of 39 (46%) respondents as crucial. Considering intrinsic unpredictability of research, and difficulty to assess the size of patient populations, the calculation of financial returns is found problematic. Hence, business risks for development of orphan medicines are viewed as significantly higher than for development of medicines for more prevalent conditions.

Regulatory barriers were selected as a major barrier by 28% of respondents (11 out of 39). Several respondents highlighted that health technology assessment procedures, and pricing and reimbursement policies are not well adapted for the assessment of orphan medicines, resulting in greater compliance difficulties for developers. This set of barriers seems to apply more to the situation today than to that around the time of the Regulation's introduction, when few countries had specific pricing and reimbursement policies in place for orphan medicines.

These stakeholder perspectives suggest that, **whilst the expectation of low return on investment indeed can indeed be a driver for market failure, it is by no means the sole reason**. Insufficient basic research, lack of scientific leads for product development, and the complexity of clinical trials for rare diseases all play an important part as well.

6.1.2. Addressing market failures

Whereas the previous section has shown that the problem identification was, at least in part, accurate, this section focuses on whether the measures the EU Orphan Regulation introduced were appropriate to address the problems. The primary focus herein is on the role of the market exclusivity reward.¹⁰³ Specifically, this section tests the hypothesis of whether:

- the orphan market exclusivity reward offers sponsors a way to increase their return on investment.

Unlike other innovation incentives, such as research grants, prizes or tax breaks, market exclusivity does not have an intrinsic monetary value. Rather, the idea behind offering market exclusivity as an incentive is that it extends the time

their responses are likely to be applicable – at least to an extent – to the situation prior to 2000 as well.

¹⁰³ Protocol assistance was introduced to support the accessibility of the Regulation to all potential developers. It is, however, not by itself a 'push' incentive. The economic value of fee waivers is relatively small in comparison to that of the market exclusivity and its role as an incentive is therefore also expected to be more limited.

during which the marketing authorisation holder can charge a 'monopoly rent' to recover the investment made.

The overall value of the reward is a product of two factors: 1) the period of *extension of protection* during which the sponsor can maximise its revenue ('additionality'), and 2) the *value of those revenues* above what would have been achieved without the added protection (based on the profit margin and sales volumes).

Thus, to estimate whether the market exclusivity can be a valuable incentive, it needs to first be assessed if it effectively extends the period during which the product is protected from profit-eroding competition. The data presented in Section 5.6 show that, for EU authorised orphan medicines, the market exclusivity extends the period of protection by, on average, 3.4 years but that there is substantial variation between products. **Over two-thirds (69%) of analysed products still had a primary patent or SPC protection well after the expiry of any market exclusivity.** For these products, it could thus be argued that the **additional protection offered by the market exclusivity was marginal.** It is unlikely that the market conditions for these products were significantly changed as a result of the market exclusivity.

However, **a little less than a third of analysed products was not protected by any major patent or SPC at the start of the market exclusivity period.** For this set of products, the market exclusivity is more likely to have been a valuable incentive as for these products the additional protection offered by the market exclusivity amounted to the full 10 years.¹⁰⁴

In 2008, a study was published that conducted a somewhat similar analysis of products designated as orphan by the FDA between 1983 and 2007. It found that the market exclusivity extended the maximum period of protection by an average of 0.8 years (Seoane-Vazquez et al., 2008b). Whilst the number is considerably lower than that found in our calculations for EU designated orphan medicines, it should be kept in mind that in the US the period of orphan market exclusivity is 7 years rather than the 10 years offered in the EU. Accounting for this difference of 3 years between the two jurisdictions brings the results roughly in line with each other.

The next question then is whether the additional protection offered by the market exclusivity allows marketing authorisation holders to achieve revenues above what they would have been able to realise in a competitive market. Our analyses presented in Section 8.3.2 clearly indicate that, after expiry of the market exclusivity (and any other forms of protection), the prices for orphan medicines decrease if and when generic competition occurs.

It is thus evident that in those cases the market exclusivity enables the marketing authorisation holder to charge higher prices. Moreover, these marketing authorisation holders are likely able to capture a larger share of the market (effectively the entire market whilst the product is under exclusivity) than they would have otherwise. This effect can even extend well beyond the

¹⁰⁴ Potentially more, in the case of products authorised for more than one orphan condition if the respective market exclusivity periods had different starting dates or if the product was granted an additional 2 years for compliance with an agreed PIP.

expiry of the market exclusivity as physicians and patients may be hesitant to switch to a competitor product. Thus, **market exclusivity contributes to increased revenues as a result of both higher prices and higher sales volumes.**

At the same time, the data in section 8.3.2 also show that, in many cases, generic competition does not occur for orphan medicines, even after expiry of all protections. It would nonetheless be naïve to conclude that here the market exclusivity had no economic value at all, as **it cannot be ruled out that the market exclusivity had the effect of permanently deterring all generic competition.** Particularly in very small markets, generic manufacturers may not be able to capture enough of a market share to recover their investments and would thus refrain from entering. A marketing authorisation holder cannot a priori know if and when generic competition will emerge and therefore will likely price products at a premium upon market entry. The subsequent absence of competition implies it can continue to charge this price indefinitely. One could therefore even argue that here the economic value of the market exclusivity is comparatively higher. No data are available, however, to measure this potential effect.

A 2008 study showed that, even after expiry of market exclusivity, orphan medicines face less profit-reducing generic competition overall than non-orphan medicines. (Seoane-Vazquez et al., 2008b) This suggests that, whilst the sales volume for orphan medicines may be lower than that for non-orphan medicines (though not necessarily so), the longer time during which a product can be sold without competition means that the marketing authorisation holder can maintain profit margins for longer and thus overall still make profit.

Extending on this finding, we also compared the level of competition for orphan medicines and non-orphan medicines based on IQVIA data. It finds that **for non-orphan products the level of competition increases with the level of turnover** (Table 13). However, overall a similar level of competition is seen as for the small group of orphan medicines (for 4 out of 9, see Section 8.2). This indeed confirms that **generic entry occurs relatively less frequently for products with low turnover (orphan or non-orphan).** However, as the group of orphan medicines that were no longer under market exclusivity or any other form of protection for long enough to observe generic entry, was relatively small, this conclusion is not very robust.

Table 13 Level of generic entry for newly introduced non-orphan medicines (average turnover 2008-2016 in EEA)

	< €10m	€10-100m	€100m – €1b	> €1b	All
<i>Non-orphan medicines</i>	132	81	76	53	342
<i>- with generic entry</i>	17	24	30	34	105
<i>Share</i>	13%	30%	39%	64%	31%

Source: IQVIA database

Overall, these analyses show that the market exclusivity can have a clear economic value and thus create the conditions whereby product developers can make a positive return on investment. As such, **market exclusivity can be a relevant and appropriate incentive in cases where the main barrier to product development is the limited potential to generate profits.** The extent to which market exclusivity in actuality translates into sufficiently improved market conditions to overcome the barrier of (expectations of) low return on investment cannot be derived from this analysis. What is also clear, though, is that **the relevance of the incentive varies substantially between products and in many cases may be limited.**

Additionally, as an economic incentive granted only *after* a product has been developed, it may do little to incentivise research in areas where the main barriers to product development are primarily scientific in nature. Here, a different type of incentives such as R&D grants or research tax credits ('push' incentives) could be more appropriate.

6.1.3. Role of current market conditions

Various sources have noted that the **prices of newly authorised orphan medicines have substantially increased over time.**¹⁰⁵ A recent report by EvaluatePharma notes that, over the period 2013 to 2017, the mean price of the top-100 most sold medicines with an orphan designation in the US had grown at an annual rate of 5.2% (EvaluatePharma, 2018).¹⁰⁶ The report also notes that the revenue per patient per year is highest for medicines used to treat fewer than 10,000 patients and indicates this confirms "that there is the potential for big gains in those companies willing to invest in ultra-rare diseases". Advances in our understanding of rare diseases and in diagnostic capacity have also meant that **potential treatment populations, and thereby markets, have increased in volume.**

These findings suggest that the **market for orphan medicines as it is today is a markedly different, and more profitable, one from that when the Regulation was first introduced.** Whilst this was in fact the intention of the EU Orphan Regulation (and similar frameworks in other jurisdictions), it appears that, at least in some areas, the economic conditions have changed to such an extent that it can be questioned whether public money¹⁰⁷ remains necessary to

¹⁰⁵ For instance: *Why are Drug Prices for Rare Diseases on the Rise?*

<https://www.healthline.com/health-news/critics-orphan-drug-law-ripe-for-abuse#1> (Accessed 12 March 2019);

Rising Orphan Drug Prices: Is there An Inflection Point for Payers?

<https://invivo.pharmaintelligence.informa.com/IV005214/Orphan-Drug-Pricing-And-Reimbursement-Challenges-To-Patient-Access> (Accessed 12 March 2019)

¹⁰⁶ Under the US Orphan Drug Act medicines that are authorised for both orphan and non-orphan indications can be sold under the same marketing authorisation. Therefore, sales on products with a US orphan designation also can include sales for non-orphan indications, as is the case for various high-selling US orphan medicines.

¹⁰⁷ Public money herein refers to the money that the EC and Member States contribute to the implementation of the EU Orphan Regulation framework (e.g. the costs for fee waivers and discounts, but also the staff costs at the EMA and COMP), as well as to the costs that health payers and patients bear as a result of the orphan market exclusivity.

attract commercial activity. At the same time, however, annual turnover levels of many orphan medicines remain below €10 million. Even though this may be counterbalanced somewhat by the lower level of competition once protection has ended, it implies that **the measure to extend the period of protection through market exclusivity still remains relevant for orphan medicines with lower turnover levels.**

6.2. Availability of and access to orphan medicines in the EU/EEA

As discussed in Section 2.2, it is clear that at the time the EU Orphan Regulation was introduced there was not only a problem with the development of treatments for rare diseases, but that also whatever products were available were not reaching all the patients in need of them: access was highly unequitable across the EU and there were substantial differences in the speed with which products would come to market, if at all.

This section explores to what extent these problems persist today, and what the underlying causes of this are. In doing so, it provides a basis for determining whether relevant actions have been taken and whether these remain appropriate.

Specifically, this section looks into:

- How does availability of, and access to orphan medicines vary across the EU/EEA?
- What are the main causes of variability?
- How, if at all, does the EU Orphan Regulation seek to address this variability?

In this study, **availability has been defined as the presence of a medicine in a particular market**, either because its marketing authorisation holder launched the product there directly, because it comes onto the market through parallel import, or because a medicine is available through compassionate use or named-patient programmes. This therefore does not account for factors related to the price of a medicine, whether it is reimbursed or whether individual patients can obtain this from their health care provider or pharmacy. Rather, these factors determine whether a patient has **access** to a medicine once it becomes available (i.e. availability is a condition for access but does not itself guarantee access).

In our analyses, **we have used sales data (obtained from IQVIA) as a proxy for availability**. This is by no means a perfect indicator, as it does not provide insight into how many patients were unable to access a medicine for financial or other reasons, and may not register use of medicines obtained outside of the standard procurement and supply chain for pharmaceutical products.

From the available data, it was not possible to quantify access. This would have required additional information on the total eligible patient base, as well as on information contained in the prescription notes, such as dosing and frequency. Access has therefore only been discussed from the perspective of patients and healthcare professionals, without triangulation with quantitative information.

6.2.1. Variations in availability and access

There are two important aspects to consider when discussing availability. The first is whether the product becomes available *at all* at any point in time, whereas the second is *when* the product becomes available (time to market).

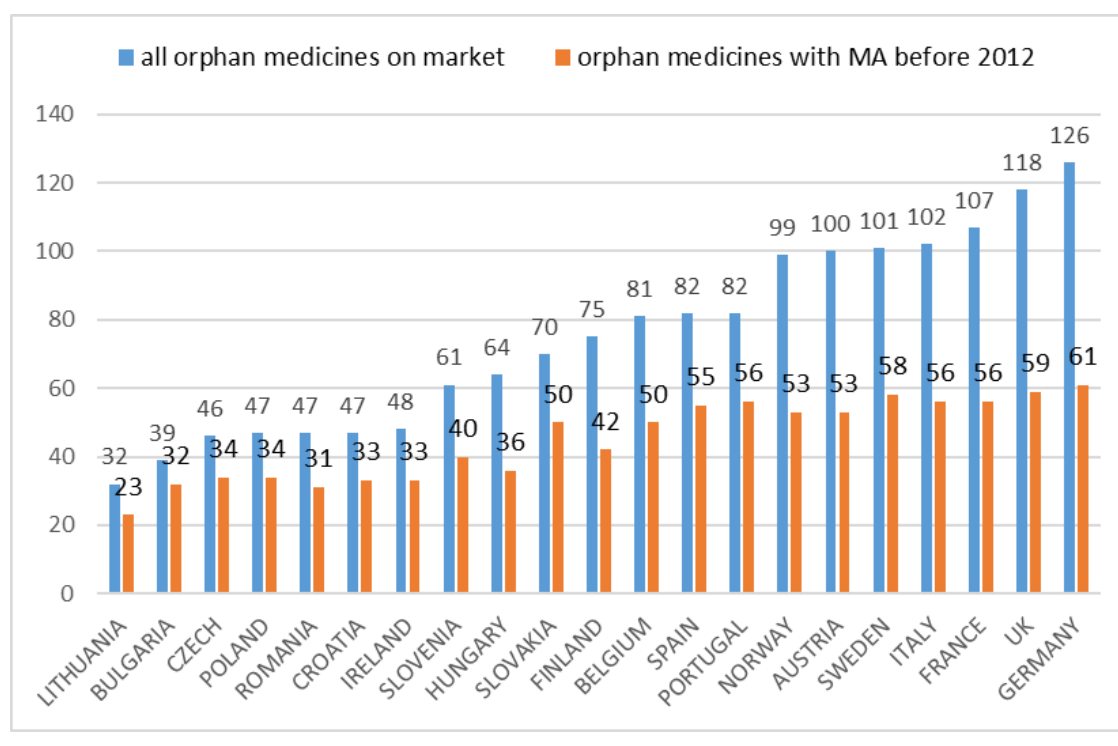
To analyse differences in availability of authorised orphan medicines between EU/EEA Member States, we have looked at the number of products (including withdrawn products) that have, at any point in time, been on the market in any country in the region. Availability herein is measured through sales data from IQVIA (2008–2016), where any sales figure larger than zero is considered indicative of availability of a medicine on the market¹⁰⁸.

This analysis shows that **the number of orphan medicines on the market in at least one EU Member State stood at 126 in 2016** (Figure 32). Some of these products have since been withdrawn from the community register of orphan medicines, but they remain available for treatment of patients with rare diseases. In this data set, countries such as Germany, the UK, France, Austria, Sweden and Italy all have a high penetration of orphan medicines in their markets with more than 100 orphan medicines available. This suggests that the regulatory and policy environments as well as market conditions in these countries may be favourable and barriers to market access are relatively low.

Figure 32 also shows availability of medicines that had received marketing authorisation before January 2012 (orange bars). For these medicines there is much less variation in availability between EU Member States.¹⁰⁹ This illustrates that, even though there are significant differences and some Member States (like Germany) are reached almost immediately and others lag far behind, in due time many of them do still reach the other EU Member States (like Lithuania and Bulgaria).

¹⁰⁸ Please note that the IQVIA-database provides only partial information for some countries. For example, for the Netherlands, Latvia, Greece, Luxembourg and Estonia the dataset only contains retail sales. See Appendix F (Part 1) for more details.

¹⁰⁹ In statistics the standard deviation is used to measure variance in a given set of data. It expresses the extent to which data differ from the mean of the data set. Whereas the mean for present number of orphan medicines in EU Member states is 75, the standard deviation is 27 (or 36% of the mean). For the number of orphan medicines present with market authorisation before 2012, the mean is 45, while the standard deviation is 11.5 (or 25% of the mean). Therefore, the spread is lower if only the “older” orphan medicines are considered, both in absolute and relative terms.

Figure 32 Number of orphan medicines for which sales were observed in 2016 (IQVIA) by Member State

Source: analysis of IQVIA data, 2018 (including withdrawn and expired orphan medicines); note: total number of observed orphan medicines (including products withdrawn) in the dataset is 129. Data for Cyprus, Denmark, Iceland, Liechtenstein and Malta are not included in the dataset. Because of limitations of the database (sampling issues) data for Estonia, Greece, Latvia, Luxembourg and The Netherlands are excluded from the analysis.

A comparable analysis was performed previously by Detiček in 22 European countries (Detiček, Locatelli, & Kos, 2018). Here, a medicine was considered available if uninterrupted sales within a 1-year period were detected. It found that, from 2005 to 2014, 125 medicines were authorised for rare diseases (of which 71 had an EU orphan designation). Between 70 (63%) and 102 (91%) products were available in Germany, the United Kingdom, Italy, France, and the Scandinavian countries, consistent with our own findings. By contrast, only 27% to 38% of these authorised medicines were available in Greece, Ireland, Bulgaria, Romania, and Croatia.

Within the scope of this study, it was not feasible to analyse whether there are particular health system characteristics that, at least in part, contribute to the observed differences in availability between Member States. Possible contributing factors are to what extent a system for health technology assessment is used and what criteria are applied therein, the number of actors involved in a health system (e.g. a national single-payer health system versus a privatised system with multiple payers), and overall health expenditure.

Stakeholder experiences with and perspectives on availability and access

Experiences with local availability of orphan medicines were examined using targeted consultation (surveys) with representatives of different groups. First,

they were asked to comment on the extent to which orphan medicines had been placed on the market directly by marketing authorisation holders. Among academic experts and representatives of patient and consumer organisations around half felt unable to estimate this (Table 14). Where estimates were given, these ranged from less than 25% to over 75%.

When asked to also take into account availability through other means, such as via parallel import or compassionate use programmes, estimates of availability increased somewhat with around a third of all respondents estimating that over 75% of products are available.

As the overall sample sizes in both groups are small and respondents do not cover all EU Member States, it is difficult to draw firm conclusions about variations in market availability between countries. Some respondents clarified that, whilst in theory most of the orphan medicinal products are available on the market, access is limited due to high prices. They also pointed out particular measures to promote rapid access through compassionate use programmes¹¹⁰ (e.g. in Denmark) or via the French Temporary Use Authorisations scheme¹¹¹.

Table 14 Stakeholder assessment of extent to which products are placed on the market in a respective country

Respondent group	< 25%	25–50%	50–75%	> 75%	Do not know / NA
Academic researchers and experts (N=29)	2 (7%)	4 (14%)	3 (10%)	4 (14%)	16 (55%)
Patient and consumer organisations (N=13)	2 (15%)	0 (0%)	2 (15%)	2 (15%)	7 (54%)

Source: Targeted stakeholder surveys. NA = not applicable

The question of availability of orphan medicines was also posed in the online public consultation to people with a direct personal experience with a rare disease and to health care providers. In both groups, over 80% indicated that, in their experience, such medicines are available in their country of residence, at least “to a certain extent” (Table 15). Around 17% of respondents in both groups stated that these medicines are “not very much” available.

¹¹⁰ “Compassionate use is a treatment option that allows the use of an unauthorised medicine. Under strict conditions, products in development can be made available to groups of patients who have a disease with no satisfactory authorised therapies and who cannot enter clinical trials. [...] Compassionate use programmes are coordinated and implemented by Member States, which set their own rules and procedures.” Compassionate Use, EMA (2019). <https://www.ema.europa.eu/en/human-regulatory/research-development/compassionate-use>

¹¹¹ The French scheme of Temporary Authorisation for Use, https://ec.europa.eu/health/sites/health/files/files/committee/stamp/stamp_stamp_agenda_point_4_fr_tau_en.pdf

Table 15 Availability of orphan medicines in stakeholder's countries of residence (online public consultation)

Respondent category	Yes, very much so	Yes, to a certain extent	Not very much	Not at all	Don't know / No opinion
Individuals with experience of rare diseases (N=105)	38 (36%)	47 (45%)	17 (16%)	1 (1%)	2 (2%)
Health care professionals (N=40)	13 (33%)	20 (50%)	7 (18%)	0 (0%)	0 (0%)

Source: Technopolis Group. (2019). Online public consultation.

Both groups were also asked about their personal experiences with the availability of orphan medicines in their country of residence (Table 16). Around a third (33%, 13 out of 40) of health care practitioners had ever encountered a situation where they had been unable to prescribe an existing orphan medicine because it was not available in the country where they practice. By comparison, over two-thirds (70%, 73 out of 105) of individuals with experience of rare diseases had experienced, or knew someone who had, a situation where they had been unable to obtain an orphan medicine because it was not available in their country of residence.

Table 16 Experiences with availability of and accessibility to orphan medicines in country of residence

Respondent group	Consultation question	Yes	No	Don't know / NA
Individuals with experience of rare diseases (N=105)	Have you, or someone you know, ever been unable to obtain an orphan medicine because it was not available in your/their country of residence?	73 (70%)	23 (22%)	9 (9%)
Health care practitioners (N=40)	Have you ever been unable to prescribe an existing orphan medicine because it was not available in the country where you practice?	13 (33%)	14 (35%)	13 (33%)

Technopolis Group. (2019). Online public consultation.

The analyses of the IQVIA data, as well as the observations from stakeholders collected in interviews and surveys, confirm that **whilst overall availability of orphan medicines in the EU has improved, there remain considerable differences between Member States in availability of, and access to orphan medicines.**

Whereas the discussion up to now has focussed on whether products eventually become available to patients, **important concerns also exist regarding when products become available.** Many of the aforementioned factors influence not only overall access but also the speed of access. For instance, access can be delayed when decision-making is contingent on the outcomes of health technology assessments or on price negotiations between marketing authorisation holders and payers. In the data presented previously (Section 5.8), Figure 31 showed that, whilst in some countries products are launched

almost immediately upon authorisation, in others it can take over 2 years (if at all).

Representatives of national public authorities were asked to estimate the average time to market entry for orphan medicines in their country from the moment of initial marketing authorisation (Table 17). A third (n=11, 32%) estimated that this takes more than six months. Similar estimates were provided by representatives of patient and consumer organisations and by academic researchers and experts. Overall, around a quarter (n=21, 28%) of respondents report delays in excess of half a year.

In clarifying comments, respondents attributed these delays to factors such as difficulties in obtaining sufficient clinical data to support HTA processes and reimbursement decisions, the time needed for assessors to review the submitted data packages, and the need for price negotiations.

Table 17 Estimated average time to national market from marketing authorisation

	Before MA*	<2 months	2-6 months	>6 months	Do not know
National public authorities (N=34)	3 (9%)	2 (6%)	6 (18%)	11 (32%)	12 (35%)
Patient and consumer organisations (N=13)	1 (8%)	0 (0%)	1 (8%)	4 (31%)	7 (54%)
Academic researchers and experts (N=29)	3 (10%)	1 (3%)	4(14%)	6 (21%)	15 (52%)
All (N=76)	7 (9%)	3 (4%)	11 (14%)	21 (28%)	34 (45%)

Technopolis Group. Surveys (2018). MA = Marketing Authorisation. * Availability prior to marketing authorisation is possible in the case of, for instance, compassionate use programmes.

Representatives of patient and consumer organisations were asked what factors in their opinion will have the largest impact on access to medicines for rare diseases in the next 10 years. Most respondents foresee that in the next 10 years new regulatory processes will have the greatest impact on the access to medicines for rare diseases. New approaches for pricing and reimbursement, such as 'pay for performance' and conditional reimbursement, and increased emphasis on value assessment and 'gatekeeping' measures by payers are expected to have a large impact on access to medicines, according to 6 (46%) and 5 (39%) respondents respectively.

6.2.2. Causes for variations in availability and access

As evidenced by the above, availability in one Member State does not imply that a medicine is also available to patients in another country. In fact, in none of the EU/EEA Member States were all authorised products available to patients at some stage. This means that **theoretical availability resulting from the authorisation frequently did not translate into access to that medicine for patients.**

There are various reasons for differences in availability of and access to orphan medicines across countries. The following sections review some of these reasons from the perspective of different stakeholders involved.

Policies for assessing orphan medicines

Whilst the increasing number of orphan medicines that are authorised is much needed and welcomed, the authorisation is merely one-step in the process that leads to the product ending up with the patients in need of it. Along the way, there are various 'gatekeepers'. The first set of gatekeepers are commonly those parties that have a responsibility for safeguarding the affordability of the health care system. As part of this responsibility, they will decide what products will be provided and paid for (at least in part) by the public health care system or by health insurance funds. Ministries of Health are typically involved in laying down the policies and criteria that determine how public funds can be directed for pharmaceutical products. Many ministries are assisted in the implementation of these policies by executive agencies that conduct a health technology assessment (HTA).

Each Member State has a different perspective on what constitutes value and thus will demonstrate a different willingness-to-pay. Some may take the view that all patients deserve treatment and put precedence on products that treat the greatest health need, regardless of their budget impact. Others value equity by paying a similar price for a unit of health production (e.g. a Quality-Adjusted Life Year, or QALY) irrespective of the unmet needs, thus looking at maximising health outcomes in the face of budget constraints (Young, Soussi, Hemels, & Toumi, 2017). Thus, whilst in some countries orphan medicines may be exempted from any value assessment and are automatically admitted into the reimbursement system, at least for a limited period of time (e.g. Germany), in most others this is only true for certain therapeutic indications or not at all.

Survey data provided by representatives of national public authorities, indicate that **in the majority of participating countries (64%) the value assessment system for orphan medicines is not inherently different from that for other innovative medicines.** In 60% of the responding countries, some form of HTA is carried out. Review of the literature, furthermore, shows that, whilst some HTA agencies and payers have created orphan medicine-specific assessment mechanisms, more often reimbursement decisions regarding orphan medicines are made following the same processes as for other medicines (Annemans et al. 2017).

The core clinical information considered by HTA agencies is broadly similar across Member States, but there are considerable disparities in what analysis methodologies are used, how data is interpreted, the perspective of the evaluation and the extent to which patients and healthcare professionals are involved (Annemans et al., 2017)(Annemans et al., 2017)(Annemans et al., 2017) Furthermore, **differences in various cost elements** (e.g. need for hospitalisation, type of health care providers involved in delivery of the treatment) **can lead to very different outcomes** for the costing element of the assessment. A further discussion on the role of national HTA processes and the need for alignment is provided in Section 9.5.2.

This study did not compare the availability of orphan medicines in the EU/EEA to that in other jurisdictions, in particular the US. In Section 5.2.1, it was discussed that the number of orphan medicines approved annually is higher in the US than in the EU. A study by Murakami et al. also showed that the median

approval time for orphan medicines in the EU is six months after that in the US (Murakami & Narukawa, 2016). However, no data were analysed in this study that would allow determination of to what extent product launch in the US market leads to greater or faster availability of those medicines for eligible patients in practice. It is likely that, similar to the national differences observed in the EU, there may be substantial differences between groups, based on factors such as coverage of health insurance and health care providers. Although, unlike most EU countries, the US does not currently have a national HTA framework, the interest in value assessment of medicines has been said to be growing here too (Pizzi, 2016).

Role of financing and reimbursement systems

The outcomes of HTA procedures will inform to what degree payers are willing to reimburse a particular treatment or may form the start of a negotiated procurement procedure. However, even once a decision has been made to (partially) reimburse an orphan medicine, **differences in financing and reimbursement systems can further influence whether and when patients are able to access a treatment.**

The survey results find that, **in most participating countries (82%) the way in which reimbursement for orphan medicines takes place is not different from that for non-orphan products.** Financing usually comes from of a combination of sources, such as national health budget, hospital budgets and/or health insurance budgets. In around a third of responding countries (32%) out of pocket payments apply. In 50% of the countries, conditional reimbursement systems exist. A similar group of countries have named-patient programmes or compassionate use programmes. In 55% of the countries that provided survey data negotiated procurement was said to exist.

A review of the literature shows **substantial differences between EU/EEA Member States in how orphan medicines are paid for and the degree to which they are reimbursed.** Countries like Germany, Finland, Sweden and France – which all have large numbers of orphan medicines available in their markets – grant full or substantial reimbursement from public resources (Detiček et al. 2018). Also France and Belgium have considerable reimbursement. Countries like Bulgaria, Croatia, Czech Republic, Hungary, Romania, Poland, Slovakia, and Slovenia have special reimbursement regimens that cover the total costs for most orphan medicines. In contrast, in Greece, medicines are reimbursed only if they are cost-effective and patients must provide a copayment when the reference price is exceeded. In the Netherlands reimbursement may be restricted to a specific indication (Denis, Mergaert, Fostier, Cleemput, & Simoens, 2010a).

Non-authorized products are available on a named-patient basis in all countries and may be imported by internationally operating pharmacies (Blankart & Stargardt, 2010). Compassionate use and off-label use is allowed, for instance, in France, the Netherlands and Italy (Denis et al., 2010a; Handfield & Feldstein, 2013). Since 1992, France has had a compassionate use system in place by which it can grant a temporary use authorisation, which authorises unlicensed medicines on an exceptional and temporary basis. The system is, however, not restricted to orphan medicines. By contrast, Sweden does not have any legislation covering compassionate or off-label use (Denis, Mergaert, Fostier,

Cleemput, & Simoens, 2010b). Medicines imported on a named-patient basis are not usually reimbursed by public health insurance (Blankart & Stargardt, 2010).

Particularly because of the high costs of many orphan medicines, whether a patient is able to access a treatment depends a great deal on whether it is fully reimbursed by the health system or if personal (co-)payments are required. In the online public consultation, individuals with experience with rare disease and health care providers were asked about their own experiences with affordability of (specific) orphan medicines. Health care professionals were asked if they had ever been unable to treat patients with a specific orphan medicine because the medicine was not (fully) reimbursed by the health care system and, as a result, was unaffordable for patients. A quarter indicated having been in this position, while 38% had not. Simultaneously, individuals with experience in rare diseases were asked if they, or someone they know, had ever been unable to obtain an orphan medicine because it was not affordable to them. A majority of respondents (67%) had experienced this. It should be noted that participants in the online public consultation frequently had experience with one particular rare disease and therefore would often not be able to comment on accessibility and affordability of orphan medicines in a broader sense. Nonetheless, their **responses are indicative of frequent problems in accessing orphan medicines due to their prohibitive costs and issues around reimbursement.**

Role of strategic decision-making by marketing authorisation holders

A **marketing authorisation holder may decide not to place a product on a particular market**, for instance because it does not see it as commercially attractive due to a small treatment population (potentially related to limited diagnostic capacity), or because of existing competition or treatment alternatives. In interviews, other stakeholders have also suggested that marketing authorisation holders opt to not place their products in particular markets out of concerns for parallel export.

Another factor that can influence a marketing authorisation holder's decision whether and when to place products on a particular market relates to the system of so-called '**reference pricing**'. In this system, countries determine the maximum allowed reimbursable price 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, wherein some countries are more likely to see rapid placement on the market than others.**

A recent study by Copenhagen Economics details some of the economic considerations that factor into the decision to launch a product in a particular market (Copenhagen Economics, 2018). Effectively, it is said, that the "*ex ante profit* (i.e. expected profits after entry) needs to be large enough to justify *ex ante costs* related to launch (i.e. expected entry costs)". Factors taken into account in the estimation of this balance include costs of authorisation, product registration and regulatory approval, obtaining import licences, developing distribution channels, and marketing the medicinal product (including outreach to prescribers and patients). On the other side of the equation, the key factors are market size, price and competition effects. **If, for a particular product,**

the net result of this balance is expected to be negative, companies may decide to forego product launch all together, or to delay this until circumstances have changed such that the result becomes favourable.

The study also cites various literature sources that show that there are significant differences in timing of launch between countries and that, for instance, reference pricing can have the effect that pharmaceutical companies delay launch in low-price countries to avoid having their prices in high-price markets undermined by a price referencing policy (Danzon & Epstein, 2012). These effects are not specific to orphan medicines but the market environment involving these products may be such (e.g. due to HTA requirements that delay access or result in negotiated procurement) that the balance works out negatively more often than for non-orphan products.

Perspectives on **why marketing authorisation holders decide to not launch or delay the launch of a product on a particular market** were sought from representatives of national public authorities and from academic experts. Both groups suggest that the **main reasons for this appear to be too small known patient populations** (thus representing limited economic potential) **and national pricing policies or reimbursement system characteristics.**

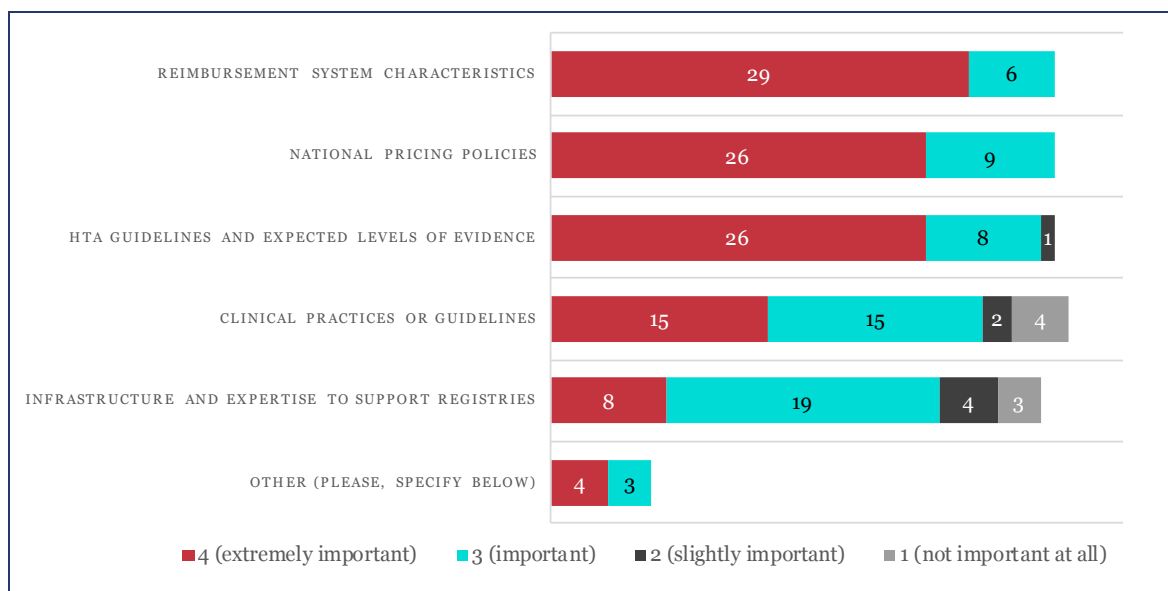
By comparison, sponsors themselves were also asked what factors most influenced their decision-making. A distinction was herein made between general market factors and factors associated with characteristics of national pricing and reimbursement systems. **Market factors most commonly cited as being 'extremely important' or 'important' were expected market size** (based on known treatment populations in a country) **and the expected level of competition** (Figure 33).

Whereas some representatives of national public authorities have suggested that the risk of parallel trade can be an important factor, sponsors themselves did not clearly identify this as such. Other reasons provided focus mainly on local pricing and reimbursement arrangements.

Various sponsors emphasised that their decision-making is informed by the ability to address unmet medical needs in a country and to offer value to patients. However, it stands to reason that for-profit companies, most of which have to answer to shareholders, are unlikely to launch products at a substantial economic loss, even when this responds to a major unmet medical need.

The role of national healthcare system characteristics in launch decision-making was addressed in more detail in a separate survey question. A large majority of sponsors considered reimbursement system characteristics (83%), national pricing policies (74%) and HTA processes (74%) "extremely important" factors in this decision-making process (Figure 33). Clinical practices or guidelines, which influence prescription of medicines, and infrastructures and expertise to support registries necessary to monitor appropriate use (sometimes a condition to reimbursement) were also viewed as important, but somewhat less so. Other reasons provided included a political climate with a social willingness to fund rare diseases and the availability of a comprehensive country strategy to address unmet medical needs from rare diseases.

Figure 33 National healthcare system factors that influence decision making by sponsors if and when to launch authorised orphan medicines in national markets



Technopolis: Survey for orphan medicine sponsors (2019).

Overall, it can be concluded that **the willingness or ability of a sponsor to launch orphan medicines in specific markets is influenced by numerous factors, both related to national healthcare system characteristics and to broader market factors. National pricing policies and reimbursement systems in particular play a large role in this.**

Role of health care providers and diagnostic capacity

Even when products have been placed on a market by a marketing authorisation holder and the medicine is (largely) reimbursed, this does not guarantee that all patients in need of a particular treatment will receive it. Further downstream there are also important gatekeepers in the form of the prescribing physicians. These need to be aware of the availability and potential benefits of a treatment to allow them to prescribe it. Usually, this would involve 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.

Representatives of patient and consumer organisations were asked, via survey, what they viewed as the **main reasons why authorised orphan medicines may not be used in their country** (Table 18). Whilst this was primarily attributed to **lack of market availability or problems with affordability, also uncertainty about the clinical benefit of the product among prescribers and unfamiliarity with the disease among health care providers and/or a lack of diagnostic capacity** were recognised.

Table 18 Perspectives of representatives of patient and consumer organisations on why authorised products are not used in the respective country

Answer category	# respondents
Product not on the market	7 (58%)
Product not sufficiently affordable	5 (42%)
Uncertainty about clinical benefit of the product among prescribers	3 (25%)
Unfamiliarity with the disease among health care providers and/or lack of diagnostic capacity	3 (25%)
Product shortages, due to issues of manufacturing or parallel trade (export)	1 (8%)

Technopolis Group. (2018). Survey for patient and consumer organisations. N=12.

6.2.3. Addressing variations in availability and access

The problem assessment underpinning the design of the EU Orphan Regulation correctly identified limited availability of and access to orphan medicines across the EU/EEA region, and variations within the region as an important contributor to the unmet medical need of patients with rare diseases. However, **as provision of healthcare and thereby also the financing of pharmaceutical products, is a national responsibility, the EU Orphan Regulation offers few tools to address this issue directly.** The main action that was taken in response, was requiring that all orphan medicines are authorised through the **centralised procedure**. This measure removes any variations resulting from national procedures for regulatory approval. As products are immediately authorised in all Member States, it in theory becomes easier for marketing authorisation holders to launch their products in all corresponding markets.

As the above discussion on factors influencing variations in market availability and access shows, though, marketing authorisation is only one step in a chain of events. Stakeholder consultations suggest that **differences in national marketing authorisation procedures were not the main source of variation even before the centralised procedure became mandatory.** As such, **the EU Orphan Regulation does not appear to be a very relevant or powerful instrument to overcome this particular challenge.**

Rather, stakeholders have suggested that, **to improve overall availability and access as well as reduce any inequities therein, measures are needed that focus on greater alignment of pricing and reimbursement policies and procedures and on joint procurement and negotiation.** This is discussed in more detail in Section 9.5.2.

6.3. Scientific developments and their potential impacts

The EU Orphan Regulation entered into force in 2000 having been designed within the context of the then state-of-the-art in research and development. Twenty years on, the field has evolved in various important ways. As previously discussed in Section 5.2 and shown in Figure 9, the number of orphan designations has sharply increased in the last decade, both in the US and in the

EU. This suggests that greater insights into the causes of rare diseases and improved know-how to support the development of new treatments are accelerating product development. Meanwhile, **new technologies, new ways of collaboration and new data sources are moving the field even further forward, with the potential to yield breakthrough treatments. These developments can bring substantial value to patients, yet they may challenge the EU Orphan Regulation framework in various ways.** It is thus timely to take stock of what the main developments have been that affect the current state of R&D for orphan medicines and to consider the extent to which these developments are likely to have affected the relevance or effectiveness of the regulatory framework.

To help prepare an inventory of scientific and sectoral developments most likely to have an impact in the field of rare disease research and the development, stakeholders were asked to identify what they considered to be the potential game changers in the coming 15 years. Academic researchers and experts, as well as representatives of patient and consumer organisations were in agreement that **advances in gene therapy, genome editing and stem cell therapy have the highest potential for impact.** Developments in molecular diagnostics, as well as in bioinformatics, big data, real world data and patient registries are similarly expected to substantially influence the field.

The following sections contain an overview of key scientific developments, based on our review of the academic and grey literature, and a review of the portfolio of EU designated orphan medicines. Where applicable, insights from the targeted stakeholder consultation have been incorporated.

These developments have been brought together into the following five categories:

1. New types of products and production techniques (Section 6.3.1)
2. New ways of conducting clinical trials (Section 6.3.2)
3. New ways of collecting data (Section 6.3.3)
4. New ways of analysing data and data applications (Section 6.3.4)
5. New ways of data sharing, collaborating and engaging with patients (Section 6.3.5)

6.3.1. *New types of products and production techniques*

As shown by the data presented in Section 5.4.4, advanced therapy medicinal products (ATMPs) account for a growing proportion of all EU orphan designations. These new products can offer many therapeutic advantages in the treatment of rare diseases. Our stakeholder consultation indicates that these medicines are expected to become even more prominent within the orphan medicine portfolio during the course of the next 10 years.

These new types of products do pose challenges in relation to the application of the EU Orphan Regulation framework, as well as from the perspective of affordability (for health care providers) and competition (high barriers to entry).

The EMA established the multi-disciplinary Committee for Advanced Therapies (CAT) in accordance with Regulation (EC) No 1394/2007, specifically to deal

with the growing importance of ATMPs within the work of the Agency overall and the challenges these new types of products pose for assessors.¹¹² The evaluation of ATMPs often requires very specific expertise, which goes beyond the traditional pharmaceutical field and covers areas bordering on other sectors such as biotechnology and medical devices.¹¹³ The CAT works closely with the EMA's other committees, including the COMP, to provide scientific advice and recommendations on each ATMP application.

The other particular challenge with the assessment of ATMPs, which is especially complex within the context of rare diseases and the work of the COMP, is that for ATMPs there is a tendency to have only **limited clinical evidence on efficacy**. This is in part because the treatment efficacy of cell and gene therapies (ATMPs) are dependent on a patient's individual genetic make-up. A 2016 study by Hanna et al. suggests that ATMPs may reach the market earlier than standard therapies due to their potential for high patient benefit, but they may do so with limited clinical data (Hanna, Rémuzat, Auquier, & Toumi, 2016). **This poses a challenge for the scientific assessors** who need to determine whether the product has a positive benefit-to-risk ratio, as well as for the COMP which needs to determine if the product offers significant benefit over existing treatment options (in cases where these exist). In discussion with the COMP, various members indicated that such scientific developments were making the assessment process more involved and more difficult.

Furthermore, due to their complexity, both in production and in the subsequent handling throughout the supply chain, biological products and ATMPs are (expected to be) more costly in comparison with treatments based on small molecules (Hanna, Rémuzat, Auquier, & Toumi, 2016). A 2011 study, for instance, estimated that the average daily treatment cost for a small molecule branded medicine was around \$1 per day, whereas that of a branded biological medicine was \$22 per day (McCamish & Woollett, 2011). **As newer generations of orphan medicines are increasingly associated with higher costs, this may pose a threat to the stated objective of ensuring a high level of health protection for all in the EU.** For ATMPs the cost implications may be harder to predict, as these may prove curative after only a single treatment or a limited number of treatments, thus eliminating the need for prolonged or even chronic administration of more traditional treatments.

Moreover, while small molecule medicines can be 'copied' relatively easily to produce generic versions (typically resulting in lower prices in the market), the composition of biological medicines is highly dependent on the expression system and conditions used to prepare these. Following the expiry of the patent/SPC and regulatory protections on a biological medicine, competing manufacturers wishing to market their own version of the product must thus demonstrate their 'biosimilar' product can be used as safely and effectively as the reference medicine. This requires a degree of clinical research

¹¹² The need for a new Committee is explained in Recital 10 of Regulation (EC) No 1394/2007 of The European Parliament and of The Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004.

¹¹³ Recital 10 of Regulation (EC) No 1394/2007.

(comparability studies¹¹⁴) that goes beyond the need to prove chemical equivalency, as would be the case typically for small molecule generics, and a **longer period of time in which the original manufacturer has an effective monopoly.**

The relative newness of biologicals and their particular challenges for would-be competitors, means **the market for biosimilars is still in its early days and may be slower to develop as compared with the market for generic medicines.** To date, the EMA has not authorised any biosimilar versions of EU-designated orphan medicines.¹¹⁵ Current orphan ATMPs have all been authorised relatively recently and are still under protection by the market exclusivity.

In relation to the EU Orphan Regulation incentives, **an extended period of market exclusivity may be relatively less valuable to developers of biologicals and ATMPs than for developers of small molecules** due to a degree of 'natural protection'¹¹⁶ these products enjoy as a result of their complexity of production. **On the other hand, incentives such as scientific advice and protocol assistance may be relatively more valuable** due to the challenges developers of these types of products face in guaranteeing their quality and safety.

6.3.2. New ways of conducting clinical trials

There has been considerable development in clinical trial design in the period since the introduction of the EU Orphan Regulation, with various novel methods being used to test interventions for rare diseases. The ambition is to overcome the limitations of traditional randomised controlled trials within the context of the small populations of rare disease patients, and thereby accelerate access to safe and effective therapies (Gagne et al., 2014).

Some efforts have focused on designs that allow for minimisation of sample size. Particular attention has focused on so-called **adaptive trial designs** which allow for modification of an aspect of the trial following a prospectively planned interim data analysis (Gagne et al., 2014). **Basket trials** enrol patients with multiple diseases and test more than one drug target in separate groups/cohorts within the same trial, making it possible to identify a potential response to targeted therapy with a relatively small number of patients (Menis et al., 2014). This clinical trial approach may streamline and expedite the development of new treatments for rare diseases (Derhaschnig et al., 2016).

The developments in clinical trial design can benefit both pharmaceutical companies and patients, by improving research productivity and accelerating the rate at which new treatments are

¹¹⁴ Biosimilar medicines: marketing authorisation. European Medicines Agency. <https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/biosimilar-medicines-marketing-authorisation>

¹¹⁵ Based on a review by the study team of all authorised biosimilars published on the website of the EMA.

¹¹⁶ By 'natural protection' we mean protection that derives from product and/or market characteristics rather than intellectual property rights or regulatory protections. For instance, for advanced therapies and biological medicines, the production may require highly specialised facilities and capabilities that are not readily available to manufacturers of generic products.

brought to market, whilst reducing the burden on patients. However, some developments in trial design indirectly affect the application of the EU Orphan Regulation and the workings of the COMP, as new types of procedures and evidence are proving challenging for the assessment process.

For example, basket trials are often designed around a mechanism of action, providing evidence on the mechanism of action rather than effectiveness per se. This can be problematic during the assessment of the benefit-to-risk ratio, as the marketing authorisation assessment is made on the basis of effectiveness in treatment of a particular condition. Moreover, as the sample sizes within each basket are small, the COMP may find it challenging to estimate significant benefit. Also in cases where basket trials address a novel mechanism of action that presents itself differently than described in the existing definition of the condition, this can pose challenges in the EMA authorisation procedure.

The EMA is looking to respond to these methodological developments through its adaptive pathways approach, which allows for early and progressive patient access to a medicine within the existing EU regulatory framework for medicines. Between March 2014 and August 2016, the EMA conducted a pilot project to explore the practical implications of the adaptive pathways concept with medicines under development. The evaluation of the pilot found that the approach was not applicable in all cases.¹¹⁷ However, it proved useful in therapeutic areas where evidence generation is especially challenging and where the medicine in question might plausibly address an unmet medical need in a defined population. This situation frequently applies to orphan medicines. The EMA will continue to explore the Adaptive Pathways approach with a view to developing the concept over time as more medicines in development are considered appropriate to this model. It should be noted, though, that the Adaptive Pathways approach has attracted considerable criticism as important questions remain regarding the collection and use of real-world data, the reliability of data and suitability for regulatory and HTA purposes¹¹⁸.

6.3.3. *New ways of collecting and connecting data*

The development of new orphan medicines hinges on a good understanding of the causes and physical manifestations of a disease. Insight into differences in how patients respond to treatments are important for further clinical development. Therefore, it is imperative to collect large amounts of data from a variety of sources and to effectively connect these to each other.

The European Commission recognised this need for enhanced data repositories and has encouraged and co-funded the creation of a pan-European infrastructure for rare diseases. This includes rare disease registries, patient registries and biobanks. We have described several of these initiatives in Section 5.9 of this report.

¹¹⁷ https://www.ema.europa.eu/en/documents/report/final-report-adaptive-pathways-pilot_en.pdf

¹¹⁸ Adaptive pathways: EMA still leaves open questions unanswered. (2016) IQWiG. <https://www.iqwig.de/en/press/press-releases/press-releases/adaptive-pathways-ema-still-leaves-open-questions-unanswered.7492.html>

What is important here is that the developments in Europe's data infrastructure can be helpful to sponsors in improving their applications for designation and to the COMP in supporting their assessment processes by providing new sources of data to establish prevalence.

6.3.4. New types and applications of data analysis

Big data and real-world data

The **Big Data**¹¹⁹ phenomenon has emerged as one of the most pervasive and powerful vectors for change across every aspect of society and the economy, and to an extent that could not have been fully appreciated when the EU Orphan Regulation came into force in 2000. Big Data has a potentially important role in the healthcare sector, with its capacity to advance research in personalised medicine (Panahiazar, Taslimitehrani, Jadhav, & Pathak, 2014). One particular source of data to consider is **real-world data**, defined as data derived from a number of sources that are associated with outcomes in a heterogeneous patient population in real-world settings (Annemans, Michael, & Kubin, 2007; The Network for excellence in Health Innovation, 2015).

Within rare disease research, access to a broad range of data may help to bolster the lack of information relating to the majority of rare diseases (Clarke et al., 2011). For example, it may offer a better understanding of the history of rare diseases through tracking of disease progression and allow for the evaluation of patterns of treatment and adherence (Garrison, Neumann, Erickson, Marshall, & Mullins, 2007). This in itself may generate new leads for orphan medicine development.

In addition, use of real-world data opens up the possibility of better targeted treatments. Currently, choosing the best medicine and its correct dose for the individual patient remains a largely empirical process: clinicians prescribe treatment, observe the outcome, and adjust treatment regimens and doses accordingly (Alemayehu & Berger, 2016). It has long been understood though that some patients respond better to certain therapies than others, but it is difficult to know a priori which individuals will respond to a particular treatment. Real-world data has the potential to improve the safety, effectiveness and health outcomes of patients via tailored medication and treatment-management approaches (Alemayehu & Berger, 2016; Faulkner et al., 2012). It has also been used to extend indications in highly heterogeneous conditions or add indications through off-label use (Hryy, Manuel, Cox, & Roos, 2015).

In addition to this, given the lack of randomized clinical trial level data regarding the experience of patients in a real-life setting, **regulatory authorities, payers** (i.e. governmental and private organisations that manage reimbursement and access to patient care) **and healthcare providers are increasingly turning towards this type of data to more fully evaluate the costs and benefits of new treatments** (Akhmetov, Ramaswamy, Akhmetov, & Thimmaraju, 2015).

¹¹⁹ Big Data is a term that describes a large volume of structured, semi-structured and unstructured data that has the potential to be mined for information and used in machine learning projects and other advanced analytics applications.

The **EMA's Adaptive Pathways pilot**¹²⁰, mentioned in the previous Section, was an example of an initiative where the regulator sought to make use of real-world observational data to complement data from traditional randomised clinical trials. Five orphan designated products were accepted into the first stage of the pilot.¹²¹ (European Medicines Agency, 2016).

Notwithstanding the promise held by use of real-world data, the concept has not yet been sufficiently proven (Kim & Kim, 2019). Important questions remain regarding data quality and standardisation, data management and how to interpret this type of data. It is, at this time, not yet widespread in HTA (Makady et al., 2018). Most of the limitations and concerns about the use of real-world data are not specific to orphan medicines. However, a further challenge for high-cost medicines, including many orphan medicines, can be that health technology agencies may recommend their reimbursement only for a specific subset of patients deemed most likely to benefit from the treatment. The question then arises as to whether this treatment population in practice is sufficiently representative of the potential wider treatment population to inform decision-making on further reimbursement outside of the observed population.

Personalised medicine and biomarkers

Advances in data analytics have catalysed the advancement of 'personalised medicine'. The premise of personalised medicine is based on the fact that 30% of medicines investigated in clinical trials fail because of lack of efficacy (Kola & Landis, 2004). **Stratifying patients and diseases based on molecular subtypes, then treating patients based on this subtype, can improve treatment efficacy.** Within the context of rare diseases, personalised genomic approaches are particularly relevant, as it is estimated that 80% of rare diseases have a genetic component (Thompson et al., 2014). The Health Research Theme of the seventh Framework Programme gave a specific focus to rare diseases as models for personalised medicine (Draghia-Akli, 2012)

As the understanding of the role of genes in specific diseases improves, and the costs for genetic testing decrease, **it is expected that personalised medicine will become increasingly widespread and within the next 20 years could be at the forefront of clinical applications** (Gülbakan et al., 2016). Some have raised the question of whether, with the advent of personalised medicine, in future the majority of diseases could be considered 'rare' (Ubel, 2016). This question was also raised in discussions with COMP representatives. **It is therefore timely to consider how developments in personalised medicine relate to, and impact on the framework and application of the EU Orphan Regulation.** A key concept in this regard is that of 'biomarkers'¹²².

¹²⁰ www.ema.europa.eu/documents/report/final-report-adaptive-pathways-pilot_en.pdf.

¹²¹ Stage I involved a short meeting with regulators to discuss the concept and design of the proposal and identify topics that required further discussion by stakeholders at Stage II.

¹²² The EMA 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>.

A recent study reviews the experiences of the COMP with the use of biomarkers for sub-setting of orphan conditions (Tsigkos et al., 2014). It outlines how the COMP has been assessing the use of biomarkers by sponsors in three main areas:

- to define the distinct medical condition or a valid sub-set for the designation¹²³
- to justify the intention to diagnose, prevent or treat a condition with a product¹²⁴
- to determine significant benefit¹²⁵

Whilst the study provides no numbers on how many applications involving biomarkers the COMP has assessed or approved, it offers illustrative examples of unsuccessful applications, which involved biomarkers, used to define specific orphan conditions. The authors state that, **although biomarkers can define a valid sub-set of a condition acceptable for designation, there is still a need to demonstrate medical plausibility and significant benefit in the defined condition.** They conclude that the “plausible link” requirement in particular “may be viewed as an argument against proposing subsets of non-rare conditions in the era of personalised medicine”.

COMP representatives have also stressed that in considering sub-setting based on biomarkers, the COMP needs to be adequately convinced by the sponsor that the orphan medicine would not work outside the subset it is being developed for. At the same time, it is recognised that establishing *absence* of efficacy is not commonly done. Therefore, robust evidence that a product is not efficacious outside of a specific subset is not likely to be available at the time of an initial application for marketing authorisation.

Whereas in the EU the experiences with the use of biomarkers for sub-setting are still relatively limited, in the US it is becoming more widespread, particularly in the field of oncology: a 2017 study by Kesselheim et al. demonstrated that, in the US between 2009 and 2015, 28% of oncological orphan medicines were based on biomarker-defined subsets (section 5.10) (Kesselheim et al., 2017). This represented 12% of all new oncology medicines authorised in that time period. The authors conclude that, “the increasing number of biomarker-defined subsets of more common diseases that will inevitably result [from scientific advances and uncovering of more biomarkers] should lead to a re-examination of how a ‘rare disease’ is defined in the United States to determine the applicability of the Orphan Drug Act”.

In discussion with COMP representatives, **several further challenges related to the use of biomarkers for orphan designation were brought forward.** First, difficulties may arise when the same biomarkers can be expressed across both rare and common diseases. In such cases, assessing whether the product meets the prevalence criterion could be difficult for lack of robust

¹²³ Orphan condition as described in guideline ENTR6283/Rev03)

¹²⁴ As per the provisions of Article 3(1)(a) of Regulation (EC) No 141/2000

¹²⁵ As per the provisions of Article 3(1)(b) of Regulation (EC) No 141/2000

epidemiological data. Discussion on significant benefit would then also be complicated if the orphan condition is not sufficiently specified, as it would not be clear what to consider as a comparator.

Second, it was noted that in certain tumours the presence of biomarkers might be transient and tumour-stage related. The presence of markers might also differ between biopsies taken from primary tumours or metastases. These factors may complicate designation based on biomarker presence because the patients belonging to the condition would be 'heterogeneous'.

Last, in the field of oncology, biomarkers are increasingly used in what is known as tissue agnostic, or tumour agnostic development. Here, product development is not focused on patients with a particular type of cancer but rather on any patient expressing particular biomarkers, independent of tissue or origin of the cancer. Treatments developed this way may display activity against (subsets of) multiple types of cancer. The question facing the COMP then is how to determine the orphan condition and which subset(s) to take into consideration in the application for orphan designation.

For the moment, these challenges have been identified but remain unresolved. COMP members have indicated that within the COMP **further exploration of the issue is taking place, which should inform whether additional guidance is required and, if so, what that guidance should be.**

6.3.5. *New ways of research collaboration and stakeholder engagement*

The complexity of rare disease research, where often the natural disease history is poorly described and where patient numbers are small and distributed, necessitates collaboration and knowledge sharing, arguably more so than in any other field of medical research.

In recognition of this need for improved data sharing, and the potential value of a pan-European approach to such networking, **the European Commission has helped launch various collaborative and data-sharing platforms with a focus on rare diseases.** Whilst some focus on pooling knowledge and resources from and for the research community, others are aimed at bringing together healthcare providers involved in delivering care to patients with rare diseases. Yet another type of networking organisation is formed by patient organisations. Although they serve different purposes and bring together different types of stakeholders, each initiative shares a focus on furthering research into rare diseases and improving the quality of care to patients living with these conditions.

The increasing collaboration among different groups of stakeholders in the field of rare diseases is changing the landscape as regards the ability to combine resources at a scale that makes breakthroughs more likely.

The realised and anticipated impacts of increased collaboration are mostly found in the understanding and characterisation of diseases, development of new treatments and the ability to offer good quality diagnosis and care to patients with rare diseases. As such, **the objectives, activities and (future) outcomes are entirely synergistic with the EU Orphan Regulation framework.**

The many efforts to aggregate knowledge as a means by which to improve research productivity are a natural complement to the EU Orphan Regulation's aggregation of pan-European demand for orphan medicines.

No real areas of tension were identified where increased collaboration could challenge the relevance of the EU Orphan Regulation as it stands today. If anything, such collaborations offer an additional pool of expertise upon which the applicable committees may draw to obtain input for the preparation of scientific advice and protocol assistance.

6.4. Concluding remarks on relevance of the EU Orphan Regulation

To assess the relevance of the EU Orphan Regulation, now and when it was introduced, is heavily dependent on two factors: was the problem correctly identified and is the design of the intervention appropriate to the needs?

In this section, we summarise the main findings against the applicable evaluation questions, highlighting where questions remain unresolved.

Appropriateness of the Regulation in its objectives and design

The hypotheses underpinning the problem identification and objective setting of the Regulation were tested. Our analyses suggest that the **insufficient economic interest for the industry to develop for rare diseases is likely to have been a contributor to the lack of orphan medicines being developed** at the time the Regulation was introduced. This view was shared by stakeholders from different target groups that were involved in the targeted consultation.

The role of market exclusivity in removing the (financial) barriers to orphan medicine development varies substantially between products. Whilst for some products, the market exclusivity is effectively the only form of protection against generic competition (not accounting for product and market characteristics that may offer some natural protection), for other products it confers little to no additional protection. On average, market exclusivity extends the period of protection for authorised orphan medicines by 3.4 years. The extent to which this translates into an effective means to overcome financial disincentives to orphan medicine development could not be conclusively established. However, it can reasonably be assumed that for a subset of products the market exclusivity is a decisive factor in a sponsor's ability and willingness to develop the product and bring it to market. As such, **the introduction of a market exclusivity incentive**, that allows marketing authorisation holders more time to recover their investments before competition begins to erode the profit margin, **has been a relevant and appropriate measure.**

Even today, **economic incentives appear to remain relevant** to encourage development for certain products, as low turnovers can still be observed. At the same time, it should be recognised that the **market conditions compared to 18 years ago have changed considerably**: for many companies, the orphan medicine market has become financially very attractive as evidenced by, among other things, the large number of companies that have orphan medicines in their

portfolio and the interest of venture capitalists to invest in this field¹²⁶ (Hughes & Poletti-Hughes, 2016).

In this light, it is striking that sponsors have almost never sought to obtain orphan designation on the grounds of expectations of insufficient return to justify the necessary investment. This raises the question of whether orphan designations are currently not also granted to products where one could reasonably anticipate high returns on investment simply because they meet the prevalence criterion

It is therefore **timely and legitimate to consider whether economic incentives that involve the use of public money¹²⁷ remain the most appropriate way to stimulate development of new treatments for rare diseases where the market itself already offers sponsors sufficient opportunity to recover their investments.** Such a rethink of the system however should be mindful of the fact that return on investment varies substantially across orphan medicines.

Availability of and access to orphan medicines across the EU

Since the introduction of the EU Orphan Regulation, the number of treatments for patients with rare diseases on the market has improved, with more products available in more markets. As such, it can be said that the 'gap' between patients with rare diseases and patients with more common diseases has narrowed, consistent with the objective of the Regulation.

Nonetheless, there is still a very large unmet medical need as for the large majority of rare diseases there remain no treatments available. Moreover, substantial variations continue to exist between Member States: whereas in some markets patients have access to most orphan medicines, in others very few are within reach. Variations also exist in the speed with which products are entering the market.

These observations show that **the objective of the EU Orphan Regulation to address the issue of availability of, and access to orphan medicines remains as relevant today as it was when it was introduced.** However, **the observed problem can only be addressed by a EU Regulation to a very limited extent**, as a substantial part of the observed unevenness stems from national policies and decision-making processes. In fact, as more orphan medicines are being developed, there is a real risk of increasing inequities in access to treatment for patients with rare diseases. This is because many orphan medicines are very expensive: the EvaluatePharma Orphan Drug Report 2018 estimates the mean cost of an orphan medicine at US\$147,308 (approx. €130,700) per patient per year. Countries within the EU/EEA region vary greatly in their ability and willingness to pay.

As a result, marketing authorisation holders are largely bypassing smaller and less attractive markets. Simultaneously, increasing price pressures may force

¹²⁶ <https://www.healthaffairs.org/doi/10.1377/hblog20170721.061150/full/>

¹²⁷ Effectively, the orphan market exclusivity reward is paid for by patients and health systems as the difference between the premium price charged for a newly introduced orphan medicine and the price charged for that medicine (or similar) after entry of generic competition.

more countries to adopt restrictive reimbursement policies. **Within the EU Orphan Regulation there are neither the tools nor the mandate to intervene at this level.** Therefore, **achievement of the objective would require additional policy actions**, either at the level of the individual Member States or through some form of joint action.

Impact of scientific and sectoral developments

In the nearly two decades since the introduction of the EU Orphan Regulation there have been a number of scientific developments that have, or have the potential, to dramatically alter the development of new treatments for rare diseases. These, in turn, may have consequences for the interpretation and application of the EU Orphan Regulation. Developments of great significant include those in the field of new types of products such as gene therapies, new trial designs, infrastructures for data collection, collection and analysis of new types of data, and increasing collaboration between stakeholders.

These developments mostly have a clear positive effect on the potential for developing new treatments for patients with rare diseases, by bringing together knowledge and resources and making better use of available data. At the same time, they may **challenge the framework and application of the EU Orphan Regulation.** It is important therefore for the regulatory framework to stay sufficiently up-to-date with such developments and their potential consequences, such that the framework is able to capitalise on opportunities whilst limiting potentially unwanted effects.

A **main area of tension** where the Regulation is being challenged as a result of scientific advances **relates to the use of biomarkers** to define a medical condition or a valid sub-set for orphan designation. Whilst personalised medicine holds great promise as a way to deliver significant added value to patients, in the context of the EU Orphan Regulation it is a major challenge. There is a widely held fear that personalised medicine will stretch the boundaries of the current regulatory framework by redefining what constitutes a rare disease. There is a fear among stakeholders that ultimately personalised medicine could result in all conditions being considered as rare, effectively breaking the system of the EU Orphan Regulation. Here, **the general sense was that the current framework is not adequate to accommodate the identified challenges.** The issue merits further consideration, involving an appropriate group of experts, to give due consideration to these and other major changes and their implications for the current legislation.

Another challenge posed is that stemming from **the use of novel trial designs.** These designs are increasingly giving rise to questions on **what evidence base regulatory agencies and HTA assessors consider acceptable for decision-making.** The consequences of this can be delayed or no entry of products in certain markets and increasing inequity in access to treatments for patients with rare diseases in the EU. That is not to say these novel trial designs should not be pursued, as they may in fact represent the best opportunity for collecting information in a challenging field of research. Rather, **further engagement between developers, regulators and downstream decision-makers is needed to understand how these designs can best be used to accelerate access to innovative (orphan) medicines in a way that**

safeguards their safety and effectiveness and whereby cost-effectiveness can be assessed.

7. Effectiveness

The EU Better Regulation guidelines for evaluation offers the following guidance for assessing the **effectiveness** of EU actions:

Effectiveness

Effectiveness analysis considers how successful EU action has been in achieving or progressing towards its objectives. The evaluation should form an opinion on the progress made to date and the role of the EU action in delivering the observed changes. If the objectives have not been achieved, or things are not on track, an assessment should be made of the extent to which progress has fallen short of the target and what factors have influenced why something hasn't been successful or why it has not yet been achieved. Effectiveness analysis should seek to identify the factors driving or hindering progress and how they are linked (or not) to the EU intervention. Consideration should also be given to whether the objectives can still be achieved on time or with what delay. The analysis should also try to identify if any unexpected or unintended effects have occurred.

Source: Better Regulation Toolbox, #Tool 47.

Thus, the effectiveness of the EU Orphan Regulation can be derived from the relation between the observed effects (i.e. products designated and authorised, R&D activity, and industry competitiveness) and the stated objectives. The objectives, identified in the intervention logic presented in Figure 4, Section 3.2, can be summarised as providing access to safe and effective treatments for rare diseases to all by stimulating the development of such treatments and promoting better functioning of the internal EU market.

Specifically, this chapter addresses the following evaluation questions:

- How have the developers made use of the specific incentives provided by the Regulation and what were the reasons behind this?
- To what extent is the Orphan Regulation effective in addressing unmet medical needs?
- To what extent has the (additional) incentive for the development of 'orphan paediatric medicine' resulted in new medicinal products catering for an unmet medical need for children?
- To what extent the Orphan Regulation and its implementation contributed to the general objective of competitiveness of European pharmaceutical industry? What were factors supported or hindered attaining this objective?
- Are the provisions of the Orphan Regulation sufficiently explicit as to when market exclusivity should be granted and revoked?

To address these questions, this chapter has been divided into five main sections. Section 7.1 assesses the uptake of different incentives and how this has impacted the effectiveness of the Regulation. It thus considers whether incentives are associated with improved rates of successful development of

orphan medicines. This discussion relates to the Regulation's objective (Section 3.2) of providing incentives for industry to develop and market orphan medicinal products.

The question of whether the Regulation has contributed to addressing unmet needs is the focus of Sections 7.2 and 7.3. The first examines the portfolio of all designated and authorised orphan medicines in terms of product characteristics (innovativeness, therapeutic areas, indications and disease prevalence) and attempts to relate these to unmet medical needs. However, as development of products is by itself insufficient to address unmet needs, Section 7.3 analyses the extent to which products are available in different markets.

Section 7.4 looks at whether the products developed under the EU Orphan Regulation effectively serve the needs of children. Together, these three sections review progress against the Regulation's objectives to ensure a high level of health protection for all, ensure the same quality of treatment to patients with rare diseases and to restore the equilibrium between supply and demand.

Section 7.5 centres on the effect of the Regulation on the landscape for R&D for rare diseases and orphan medicines in the EU. This links directly to the Regulation's objectives of ensuring a better functioning of the internal market, preserving fair competition and encouraging innovation.

The final section of this chapter, Section 7.6, is focused primarily on whether the regulatory framework is effectively implemented by considering under what conditions the incentive of market exclusivity is granted. This is more a procedural effectiveness issue and as such is not clearly linked to one of the Regulation's objectives as set out in the intervention logic.

7.1. Role of the specific incentives provided by the Regulation

To appreciate the impact the EU Orphan Regulation has had on the development of new treatments for rare diseases, it is first necessary to understand to what extent stakeholders have engaged with the Regulation. If incentives are not used, after all, they cannot be expected to make any impact.

This section discusses to what extent stakeholders have made use of specific incentives provided by the Regulation, and what role these incentives can play in supporting the development of orphan medicines.

7.1.1. Uptake of incentives

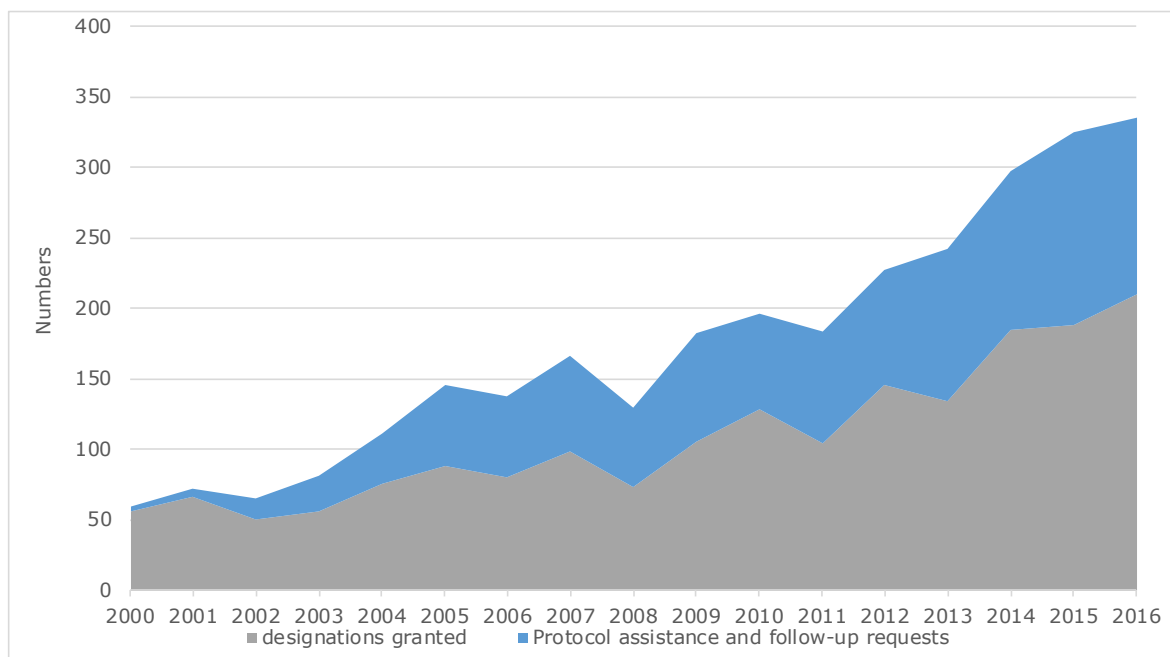
Section 5.3 provided data on the use of protocol assistance during product development, on the number and types of applicants and sponsors that benefitted from fee waivers, and on how many times market exclusivity was granted to authorised orphan medicines.

Protocol assistance

The **uptake of protocol assistance has increased markedly over time**: from only a handful in the first few years to over 125 requests per year in 2017 (Figure 34). This trend has closely followed that in the number of designations granted. In a survey among developers, protocol assistance was widely deemed 'very important' (54%) or 'important' (18%). Only 5% of respondents indicated did not consider protocol assistance important to them.

The increasing share of SMEs (Section 5.7, Figure 14) among applications for protocol assistance concurs with the observation that SMEs now account for around half of all designations annually (Figure 28), and thus is an expected result.

Figure 34 Relation between number of designations and protocol assistance



Source: EMA data, 2018

These quantitative findings by themselves do not provide any insight into for whom protocol assistance is most important or effective. Interviewees from industry have suggested that protocol assistance is most valuable to relatively inexperienced developers. In general, developers of products for which demonstration of significant benefit is required stand to benefit from protocol assistance.

Various studies have been conducted to see whether uptake of protocol assistance is positively correlated with higher chances of successful development. A 2009 study aimed to **identify predictors for successful marketing authorisation of orphan medicines** in the EU (H.E. Heemstra, van Weely, Buller, Leufkens, & de Vruh, 2009). Based on data for the period 2000-2006 the authors observed that (1) in April 2005 80 protocol assistance procedures were completed and only four approved orphan medicines obtained protocol assistance, and (2) from the 31 authorised orphan medicines in October 2006, only seven received protocol assistance. Based on these observations they did not identify protocol assistance as a predictor for a successful marketing authorisation. Rather, they found that approval of orphan medicines was strongly associated with previous experience of the sponsor in obtaining approval for another orphan medicine.

Another study by Putzeist et al. (2012) also did not find a positive association between protocol assistance and successful marketing authorisation. Here, the

only critical success factors identified were (1) clinical trial characteristics, (2) the selection of a clinically relevant endpoint and (3) providing representative target population data as pivotal study evidence.

More recently, a study looked into whether uptake of and compliance with scientific advice is associated with a positive orphan medicine marketing authorisation outcome, using data over the period 2000-2013 (Hofer et al., 2018). This analysis shows that compliance with the scientific advice provided by the Scientific Advice Working Party (SAWP) or Committee for Medicinal Products for Human Use (CHMP) was one of the most important determinants for a positive orphan medicine marketing authorisation outcome. For products where the sponsors complied with the scientific advice, 80% successfully achieved marketing authorisation. Among products for which the scientific advice was not complied with, only 36% were authorised.

Regnstrom et al. (2010) also identify factors associated with a successful marketing authorisation, but not specifically for orphan medicines. This study too concludes that compliance with scientific advice is a predictor of a successful outcome (Regnstrom et al., 2010a)

Taking an opposite approach, Heemstra et al. (2011) aimed to identify characteristics of orphan medicine applications, which *failed* to achieve marketing authorisation in the US. They conclude that there are three main factors associated with non-approval: (i) the clinical trial design, (ii) the level of experience of the sponsor and (iii) the level of interaction with the FDA (i.e. early FDA review, FDA advice on design and conduct of the trials). For the latter factor, the authors found that the probability of non-approval for sponsors not adhering to the FDA-advice was significantly higher compared to sponsors who did follow the advice.

Thus, **whilst recipients value protocol assistance as an incentive, its role in improving the likelihood of successful orphan medicine development is inconclusive.** It is nonetheless likely that compliance with protocol assistance facilitates the regulatory assessment by assisting sponsors in assembling a more robust dossier of relevant clinical trial data. A representative of a patient and consumer organisation also highlighted that, in their experience, the scientific advice and protocol assistance for orphan medicine developers have aided in improving the design of clinical trials for the benefit of patients, as the provision of the advice often involves a consultation of expert patients.

Fee reductions

Section 3.3.5 details what fee reductions apply to whom and showed the overall expenditure on fee reductions over the period 2000-2017. In a survey, most industry stakeholders viewed these reductions as 'important' (34%) or even 'very important' (34%). Further exploration of the issue in interviews with developers suggests that the importance of fee reductions is higher for SMEs (for which fees can be waived completely) than for large pharmaceutical companies for whom such fees are a relatively minor cost.

Of note is that, in its system of fee reductions, the EMA only distinguishes between two types of applicants: SMEs and non-SMEs. For the former all fees are waived completely. Others still pay fees for non-paediatric related protocol

assistance (75% reduction), and for the initial marketing authorisation application (10% reduction).¹²⁸ Therefore, any entity not listed on the EMA's SME Register will still incur some costs from the procedures and services associated with the EU Orphan Regulation.

The idea here appears to be that there exists a broadly binary classification between types of sponsors: SMEs on the one hand, which may have less access to financial resources, and large pharmaceutical companies with significant resources at their disposal on the other. **This classification, however, does not reflect the reality that sponsors are also found outside of these two categories**, as was shown in Section 5.7. To be considered as an SME¹²⁹, an entity must meet the criteria set out in Commission Recommendation 2003/361/EC.¹³⁰ This includes, among other things, that "proof of establishment of the company in the EU/EEA" is provided, "for example inclusion in a commercial register as a permanent legal structure." It was noted in interviews that **for some types of sponsors, such as charitable foundations (e.g. the Telethon Foundation¹³¹) and academic institutions, it can be difficult to meet the requirements for SME status**. Yet, these organisations do not have the same kind of resources that large pharmaceutical companies do, and for them the EMA fees can still be significant.

The information collected from developers suggests that fee reductions and waivers play a role in lowering the barriers to access other services provided by the EMA in support of orphan product development, in particular protocol assistance. **No data are available, however, to determine whether these fee reductions and waivers make an appreciable impact on the number of products under development**. The very fact that relatively small¹³² sponsors are still found to apply for designation, even when they do not qualify for the reductions offered to SMEs, suggests that – compared to the overall costs of R&D – the EMA fees need not be an unsurmountable barrier. This, however, does not mean the fee reductions have no role to play in the overall package of incentives the EU Orphan Regulation offers. It is not known how often these fees do represent a real barrier to potential sponsors.

Market exclusivity

As shown by the data provided in Section 5.3.1., from the moment the EU Orphan Regulation went into effect until the end of 2017, **market exclusivity**

¹²⁸ EMA (2014), 'Executive Director's decision on fee reductions for designated orphan medicinal products', (applicable on October 2018).

¹²⁹ The SME status is applicable solely for EMA related activities and does not serve for other national or EU funding programmes.

¹³⁰ <https://www.ema.europa.eu/en/human-regulatory/overview/supporting-smes/applying-sme-status>

¹³¹ <http://www.tigem.it/the-institute/the-telethon-foundation>

¹³² The use of the term 'small' herein refers more to the financial resources an entity has at its disposal for these purposes, relative to large pharmaceutical companies, than to the actual size of the entity.

was granted to 142 orphan medicines. Of these, 20 were authorised for more than one orphan indication (46 indications in total) and thus were granted multiple periods of market exclusivity. Thus, **market exclusivity was granted a total of 168 times.** Marketing authorisations have also been granted to products that had at some point been orphan designated, but for which the designation was not confirmed at the time of marketing authorisation. These products therefore were not granted market exclusivity.

In the survey to developers, the market exclusivity reward was identified as the most important incentive of the EU Orphan Regulation, with 95% considering it 'important' or, most often, 'very important'. In addition, the 2-year paediatric extension to the market exclusivity was considered either 'important' (21%) or 'very important' (71%). This level of appreciation for the market exclusivity reward would suggest that it is a major contributor also to the overall effectiveness of the Regulation in bringing new treatments to market. However, the analysis presented in Section 8.3.2. indicates that the overall contribution here may be smaller than what industry stakeholders imply.

A key consideration is to what extent expectations of an *ex post* reward (that is, a reward that is received only if product development is successful and leads to a marketing authorisation) influence *ex ante* decisions to invest in R&D. Here, some interviewees from industry have suggested that it is not per se the market exclusivity, but rather the orphan designation itself that is the main incentive: this is what signals to potential investors that the product under development holds promise and is worth consideration for investment. Naturally, though, this cannot be viewed separately from the promise of economic reward that the market exclusivity reward holds. Indeed, other industry interviewees have indicated that the market exclusivity is the incentive that enables starting companies to attract venture capital. These two perspectives are complementary rather than conflicting.

It has also been pointed out that the market exclusivity does not usually influence early stage development as this is frequently done by a different set of actors than those who will eventually commercialise the product.

Overall, it appears that **market exclusivity is an important contributor to the increased levels of activity seen in the development of orphan medicines but is not the sole driver of that activity.**

Concluding remarks on uptake and effectiveness of incentives

As the above paragraphs show, **each of the incentives offered under the Regulation is a likely contributor to the impact of the Regulation. However, their relative contributions cannot be conclusively established** for several reasons:

- Incentives are used in conjunction such that there are no comparators
- The incentives work at different parts of the development process and serve different purposes
- Impacts will vary from sponsor to sponsor and from product to product.

Moreover, available information from literature and discussions with stakeholders suggest that there are many other contextual factors that play as

much, or more, of a role in shaping the outcomes of clinical development of orphan medicines. These include, for instance, the experience of the developer and the resources the developer has at its disposal, as well as certain product characteristics.

7.2. Addressing unmet medical needs

Assessing whether the Regulation has effectively addressed unmet medical needs is not a straightforward undertaking as there is no single way to define 'unmet medical need'. A 2006 Commission Regulation on conditional marketing authorisations defines unmet medical need as 'a condition for which there exists no satisfactory method of diagnosis, prevention or treatment in the Union or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those affected'¹³³ (European Parliament and Council, 2006). However, by including the wording 'major therapeutic advantage', this definition itself remains open to interpretation.

To nonetheless provide some insights into this important issue we have operationalised the concept in various ways. First, consideration is given to the extent to which products have been developed in (therapeutic) areas that can be considered 'first in class', meaning that these products – if authorised – can be reasonably expected to serve a group of patients for whom no other treatment options existed (Section 7.2.1). As more and more orphan medicines are being developed and reach the market, a connected question arises as to what benefit over existing products is offered by those products that are second or further in class.

Second, we have analysed in what therapeutic areas and for what indications products have been designated and authorised (Section 7.2.2). Whilst it cannot be said that certain therapeutic areas or indications represent a greater unmet need than others, this analysis provides some insight into what areas may be relatively underserved by the Regulation.

Third, analysis has been done into the relative rarity of the conditions for which designations have been granted (Section 7.2.3). Purpose of this was to see if the Regulation has been effective also for some of the rarest diseases or whether product development has tended to cluster around the upper-limit of the prevalence limit for eligibility.

Last, section 7.2.4 contains a discussion of how 'unmet medical need' has been operationalised by regulatory agencies by offering additional incentives, in the form of accelerated assessment, to products that are deemed particularly promising and important.

7.2.1. Product development in areas without prior activity

One of the main drivers of the EU Orphan Regulation is to ensure the quality of treatment to patients with rare diseases and thus to foster the development of products in areas where there are no good treatment options. A first

¹³³ Article 4 paragraph 2 of Commission Regulation (EC) No. 507/2006

consideration is therefore whether the Regulation has been successful in directing development to these areas.

Figure 18 in Section 5.4.2 showed that in the years immediately after the Regulation's introduction, **the number of new orphan indications per year declined rapidly**. Whereas in 2001 78% of orphan designations were for new indications (i.e. indications for which no products had been authorised), in recent years this has decreased to less than one in five designations. This is a normal and largely expected result, as product development tends to focus on areas where there are sufficient scientific leads, and activity in a particular area may signal to other developers that product development in that area is viable. Importantly, however, orphan designations were still granted for between 15 and 41 new indications each year.

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 the market exclusivity. **Owing to the increasing number of orphan medicines authorised, more and more products need to demonstrate significant benefit as the number of available comparators rises**. A 2018 analysis performed by the EMA itself of products authorised between 2000 and 2015 showed that demonstration of significant benefit was required in 64% of designations and for 73% of products¹³⁴ at the time of marketing authorisation. Among products for which demonstration of **significant benefit** was required, this **was granted most often on the grounds of 'improved efficacy'**¹³⁵ **(87% of all significant benefit grounds at marketing authorisation)**, particularly in sub-populations (Fregonese et al., 2018). Improved safety was a ground in only 8% of cases. Significant benefit based on a major contribution to patient care, such as new formulation routes that improve ease of use, was granted at the time of marketing authorisation in just eight cases.

Together, these observations indicate that **with time the EU Orphan Regulation is becoming less effective in directing research to areas where there are no treatments yet**. At the same time, for certain conditions the number of treatment options is expanding and the market here is starting to look more and more like that for non-orphan medicines. This in itself is of value to patients with those specific conditions, for whom the need can increasingly be considered 'met' (though it is worth noting here that relatively few treatments are truly curative or even preventative). Nonetheless, it leaves open the question if the EU Orphan Regulation is adequately focused on supporting development in areas of greatest unmet need. Many representatives of national public authorities and academic researchers who were consulted for this study voiced concerns about the effectiveness of the EU Orphan Regulation

¹³⁴ Including separate orphan conditions that are marketed under the same tradename and products that withdrew orphan status after significant benefit was questioned by the COMP at the time of assessment at marketing authorisation.

¹³⁵ "Improved efficacy was defined as 'any evidence that the use of the new medicine will result in more efficacious treatment (or prevention or diagnosis) of the target condition as compared to the existing satisfactory methods of treatment (or prevention or diagnosis)'"

in this respect. They note that whilst the overall number of treatments has increased, this success has not been uniform.

7.2.2. Product development by therapeutic area and indications

The issue identified of product development increasingly focusing on areas where treatments already exist calls for an analysis of which therapeutic areas or indications have received more attention from developers than others. The data presented in Sections 5.4.1 and 5.4.2 showed that, although products have been designated and even authorised in nearly all main therapeutic areas (based on ATC code classification of products), the distribution has been far from even. The analysis of treatments for rare diseases and orphan-like products available on the EU market before 2000 presented in Section 2.2 indicates that this unevenness was seen already even before the Regulation went into effect.

Whilst there are several therapeutic areas that have clearly seen an above average level of (Figure 17), the one that has attracted most scrutiny is the class of products that includes anti-cancer treatments which accounts for around a third of all designations and authorised products. Also, among the six orphan indications with the highest number of designations, five target some form of cancer (Section 5.4.2). A similar degree of concentration in oncology has been observed in the US. The clustering around oncological products can be ascribed to a number of factors. The first is that in recent years, the pharmaceutical industry has shown extensive interest in the development of new anti-cancer treatments and this had led to such treatments accounting for an increasingly high proportion of all new chemical entities in development (Norman 2013). Some of these may end up being used for the treatment of rare forms of cancer, even if they were not initially developed for this purpose.

Second, **treatments for rare cancers often have broader applicability across a range of cancers**, some of which may not be considered rare. For instance, tyrosine kinase inhibitors such as *imatinib* and *nilotinib* have been investigated, and in some cases authorised, for use in a number of conditions, some even beyond the field of oncology.¹³⁶ This means that the total treatment population can be considerable, and these products thus have a higher profit potential than products that exclusively target one disease with a small treatment population. Thus, there is an incentive for developers to seek orphan designation for most oncology treatments. Moreover, anti-cancer treatments are among the most profitable medicinal products on the market.¹³⁷ **This increased profit potential likely is an important driver for product developers to focus on rare cancers**, though sponsors did not confirm this hypothesis. Rather, they emphasised linkages to existing product pipelines and the availability of scientific leads as the factors that influence where a company's R&D is focused.

¹³⁶ Nilotinib is being investigated for use in various neurological conditions such as Parkinson's, Alzheimer's and Huntington's disease. <https://medicalxpress.com/news/2013-05-cancer-drug-build-up-toxic-brain.html>

¹³⁷ See, for instance, <https://www.reuters.com/article/us-oncology-m-a/old-pharma-sees-new-profit-cure-in-cancer-drugs-idUSKCN0ZZ0BG>

Although opinions of the stakeholders varied on whether the high share of oncological products is problematic, to most people the occurrence was not surprising. Multiple interviewees raised that worldwide, also in the development of non-orphan medicines, there is a clear emphasis on cancer research. It would therefore follow that in therapeutic areas such as oncology, where there is a better-understood natural disease history and in-depth understanding of the molecular pathways involved with the disease, development of new treatments is accelerated.

In the survey, developers indicated that they are motivated largely by addressing unmet need. However, as described earlier, the definition of unmet medical need is broad. In light of the observed clustering, it would rather appear that some developers may consider any product that meets the criteria for designation as one that inherently addresses this need.

Understanding why development concentrates in certain areas is helpful, but arguably the more urgent question is why development is apparently *not* happening in other areas. **At an individual company level, survey respondents cited lack of fit with the overall company focus and R&D pipeline, and lack of scientific expertise as main reasons to not be active in other areas.** Particularly for smaller companies, there is a need to limit the scope of the product development pipeline to specific areas or indications. How this translates into an overall lack of activity at an industry level is more difficult to establish conclusively. Based on stakeholder perceptions, it seems likely that here a lack of basic research plays a part. Possibly, also the economic outlook for products in particular areas remains unfavourable even with the market exclusivity, either due to too small markets or to the complexities of product development and production.

The issue of clustering around areas and indications, and potential measures to achieve a better spread have been discussed also from the point of view of efficiency in Section 8.4.3.

Development of follow-on products

Whilst the EU Orphan Regulation, and similar initiatives elsewhere, have been credited with incentivising the development of new orphan medicines, the question has arisen whether the **orphan market exclusivity granted simultaneously poses a barrier for development of follow-on products for that same orphan indication.** This would negatively affect patients who would benefit from additional treatment options, for instance because they do not sufficiently benefit from the first authorised product.

In theory, the EU Orphan Regulation contains provisions to mitigate the impact on development of follow-on products. First, the market exclusivity for orphan medicines extends market protection only against competition by “similar medicines with similar indications”, in which a similar medicine is understood to contain “an identical active substance, or an active substance with the same principal molecular structural features (but not necessarily all of the same

molecular structural features) and which acts via the same mechanism".^{138,139} If any of these criteria is not fulfilled, the product is not considered similar. A product that contains a different active substance, or that acts on a different molecular pathway is thus not prevented from entering the market alongside the original product, even if the latter is still under market exclusivity. However, to be eligible for an orphan designation itself, that product would need to demonstrate significant benefit over the already authorised treatment. This requirement may act as a deterrent to product development, due to uncertainty about being able to demonstrate significant benefit.

Furthermore, whilst the market exclusivity bars the EMA from considering a second marketing authorisation for a product similar to one that is under market exclusivity, companies are not prevented from entering the market altogether; they are simply delayed in doing so. Nonetheless, in a market that is inherently small, developers may question whether there is sufficient willingness among patients and prescribers to switch to another product. A 2011 study found that **in areas where there are no follow-on orphan medicines, the main reasons related to time and market size, rather than to 'monopolies' created by the market exclusivity.** (Brabers, Moors, Van Weely, & La De Vruhe, 2011).

Once a marketing authorisation is obtained by a competitor product, however, this is said to be a consideration in deciding whether to continue the development of a product as, from that moment onwards, any new product that seeks authorisation for the same indication will need to demonstrate significant benefit over the first product. Our analysis of the portfolio of authorised orphan medicines finds that for 82% of orphan indications where there is at least one authorised orphan medicine, there is no other authorised orphan medicine (yet).

The survey conducted amongst developers of orphan medicines suggests that to the majority of developers of orphan medicines **the fact or likelihood of competition with another organisation does not lead to suspension, termination, refocusing or delay of new or ongoing R&D.** Survey respondents explained that "competition increases the time pressure on development and the risk to fail by coming second at the stage of marketing authorisation, but decisions to continue will depend from the clinical results".

Asked about the impact of competition on the decision to initiate or continue R&D for a product covering the same indication(s), sponsor representatives noted that it is very difficult to answer such questions, as investment decisions are very complex. The stage of development of a product, similarity of products, the quality of designed product by an organisation and its competitor will, to a

¹³⁸ Article 3C of the 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.

¹³⁹ EMA marketing authorisation and market exclusivity. http://www.ema.europa.eu/ema/index.jsp?curl=pages/Regulation/general/general_content_000392.jsp Accessed 13 January 2019.

large extent, determine whether the granting of an initial EU orphan designation or marketing authorisation to a competitor lead delay, termination or refocusing of R&D.

7.2.3. Product development by prevalence of orphan conditions

An analysis was conducted to determine the relation between designated and authorised orphan medicines on the one hand, and disease prevalence of the conditions targeted on the other. Purpose of this analysis is to better understand whether the Regulation has been effective also for truly rare diseases, or whether attention has tended to focus on diseases that are relatively more common (but that still fall within the eligibility criteria for orphan designation).

The data presented in 5.4.3 suggest that **the EU Orphan Regulation has been rather successful at promoting product development for some of the rarest diseases, where market potential is most limited**. Nonetheless, stakeholders from different target groups (not including sponsors) have suggested that the currently used prevalence threshold of 5 in 10,000 should be lowered, as they feel that, at present, the Regulation also stimulates product development in areas where there are already sufficient market stimuli. It should be noted, however, that frequently these discussions focus on products that have been authorised for more than one orphan indication. Therefore, it appears that these stakeholders are objecting primarily to the fact that the Regulation still provides incentives for products even when the *cumulative* prevalence of conditions for which the treatment has been authorised exceeds the eligibility criteria. This issue is discussed further in Section 8.4.1.

As discussed in Section 4.3.3, the calculation of prevalence itself has been the focus of debate and is often challenging. One of the COMP members has indicated in an interview that, within the COMP, it is being considered if, in the case of oncological conditions, incidence might be a more appropriate indicator than prevalence. In this context, it would use a threshold for rarity as determined by the RARECARE¹⁴⁰ project (no more than 6 in 100,000). Other COMP members have confirmed that the COMP is currently working with methodologists to establish the best methods for calculating prevalence, potentially taking into consideration the nature of the disease (e.g. acute, subacute, chronic).

The available data provide no insights into what effects the EU Orphan Regulation has had on the development of medicines in other areas that do *not* meet the designation criteria based on prevalence.

7.2.4. Conditional licensing and exceptional circumstances

Under the EU regulatory framework, conditional marketing authorisation (CMA) or authorisation under exceptional circumstances can be given (European Parliament and Council, 2006). **A CMA mandates post-marketing studies to confirm the positive benefit-risk ratio, together with demonstration of an unmet medical need or a therapeutic benefit**. It is valid for one year and can be renewed or transformed into a full marketing authorisation when the data are considered sufficiently complete. The granting of a CMA allows

¹⁴⁰ <http://www.rarecare.eu/>

medicines to reach patients with unmet medical needs earlier than might otherwise be the case, and enables additional data on the product to be generated and assessed (Mariz et al., 2014).

An **authorisation under exceptional circumstances can be granted to products for which it is not possible to provide comprehensive data on efficacy and safety under normal conditions of use** (e.g., the indication is too rare, comprehensive information cannot be provided in the present state of scientific knowledge) or it would be unethical to collect such information (e.g., bioterrorism) (Fregonese et al., 2018). An exceptional circumstances marketing authorisation does not foresee a transformation into a full marketing authorisation. Indications where applications have been submitted using this route include rare diseases where patient recruitment is difficult and mortality high (Mariz et al., 2014).

A report on 10 years of experience with CMA covering the period 2006-2016 showed that **of the 30 CMA granted, 14 were for products that were designated as orphan at the stage of initial assessment** (European Medicines Agency, 2017b). Out of 22 unsuccessful CMA applications, 16 were for products with an orphan designation. In all unsuccessful applications (both for orphan and non-orphan designated products) the CHMP considered the benefit–risk balance negative.

Additionally, Regulation 726/2004 enables developers to request Accelerated Assessment¹⁴¹ for “medicinal products of a major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation.” As there is no single definition of what qualifies as such a product, the assessment is done on a case by case basis by the CHMP. An Accelerated Assessment reduces the timeframe for the CHMP to review a marketing authorisation application from 210 to 180 days. The procedure is open to, but not restricted to, orphan medicines.

Data provided by the EMA indicate that for 30 orphan medicines with an active orphan status (i.e. with a marketing authorisation that is not expired or withdrawn), an Accelerated Assessment evaluation was requested. For 3 products (3%) such a procedure was finalised (Table 19). No information is available on the status of the other 27 procedures. Although neither the Accelerated Assessment procedure nor the CMA forms a prerequisite for the other, the EMA recommends sponsors to make use of the first when applying for the second.

What the here presented data show is that a substantial number of orphan medicines can be considered to have the potential to substantially address unmet need, even though the clinical evidence base to demonstrate their effectiveness is (for now) limited. **The true value of these products still needs to be demonstrated under real-life conditions.** Representatives of HTA institutions and Member States have indicated that the shortage of evidence at the time the CMA is granted represents a real challenge for

¹⁴¹ Accelerated Assessment, European Medicines Agency.
<https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/accelerated-assessment>

assessors who need to determine whether a product is cost-effective and should be admitted into reimbursement systems.

Table 19 Accelerated Assessment of orphan medicines

	Started Accelerated Assessment procedure	Finalised Accelerated Assessment procedure
No	74 (71%)	101 (97%)
Yes	30 (29%)	3 (3%)

Source: EMA, 2018. (N=104, all authorised orphan medicines with an active orphan status as of October 2018)

7.3. Impact on availability of and access to orphan medicines

Whilst the development of treatments is a prerequisite for addressing unmet medical need, it is of no value in itself if patients do not have access to such treatments. This section therefore reviews to what extent access to orphan medicines has improved compared to the situation before the introduction of the EU Orphan Regulation.

Comparator situation

To assess the impact of the EU Orphan Regulation on availability and access to orphan medicines, various analyses have been carried out. Together these analyses give an indication of the comparator situation, i.e. the most likely situation that would have emerged without the EU Orphan Regulation.

As shown in Figure 7, in total 142 orphan medicines received marketing authorisation in the period 2000-2017. For 11 of these orphan medicines the marketing authorisation has since been withdrawn.

Not all of the growth in the availability of orphan medicines can be attributed to the EU Orphan Regulation. Also in the situation without the EU Orphan Regulation the development of orphan medicines would have progressed. The development of medical knowledge and technology would have continued and resulted in lower production costs. Stimulating measures for development and marketing of orphan medicines that were already in place in countries such as the US and Japan before the introduction of the EU Orphan Regulation in 2000, would also have stimulated further development. And demand for medicines would have increased due to increased availability and higher household incomes.

Therefore, several analyses have been carried out to assess the size of the following types of impact of the EU Orphan Regulation:

- **Development of new orphan medicines**, which otherwise would not have been developed, neither in the EU, nor elsewhere. This relates to the group of medicines that became available due to the rewards of the EU Orphan Regulation, such as subsidies for research and development of medicines for rare diseases at EU and national level and the 10 year period of market exclusivity granted to authorised orphan medicines, on top of a patent protection, SPC and regulatory exclusivities;
- **Faster availability** in the EEA of those orphan medicines that would anyway have been developed. This relates to orphan medicines that

might have been introduced first in a market outside the EU, such as US or Japan, before introduction in one of the EEA Member States;

- A **wider spread** of orphan medicines within the EEA, as the Regulation provides a single point for marketing authorisation in the EEA. This might speed up introduction in various individual EEA markets, even though the fact that every national market has its own admission procedure has not changed.

We describe the results of the analyses on each of the three types of expected impacts below.

Development of new orphan medicines

To estimate which share of the orphan medicines authorised in the EU can be attributed to the EU Orphan Regulation, we compared the development in marketing authorisations for orphan medicines during 2000-2017 with the general market trend for pharmaceutical product development. This trend is represented by the positive opinions of the EMA on non-orphan medicines during the same period. The analysis, which is described in detail in Appendix F, shows that since 2011 the number of marketing authorisations for orphan medicines has not only grown over time, but has grown substantially faster than that for non-orphan medicines. The total extra growth is assessed at 21 orphan medicines (range 18 to 24), or an impact of almost 20%¹⁴².

To test this statistically derived impact, we also explored the potential impact of the market exclusivity reward on sales revenues of orphan medicines, and thus on the expected profitability of a development investment. This analysis shows that, **due to the market exclusivity reward, revenues from orphan medicines can be expected to be on average 10 to 20% higher**. It is not unlikely that these extra revenues have stimulated the development of orphan medicines to the extent found in the statistical analysis.

Thus, we conclude that **the number of additional Orphan medicines having been developed as a result of the EU Orphan Regulation is 18 to 24 during 2000-2017**.

Faster availability of orphan medicines in EEA

A second effect that may be expected from the EU Orphan Regulation is the faster availability of medicines catering for rare diseases in the EEA. To assess this impact a comparison has been made of the development in the time to market for orphan medicines (using information on historic orphan-like products introduced before 2000 and orphan medicines introduced after 2000) and the comparable development for non-orphan medicines.

First, an analysis was carried out of the average time it took for medicines that had been designated orphan medicines in the US ('orphan-likes') to reach the first national market in the EU ('lead time'). Analysis of IQVIA data shows that

¹⁴² We estimate that 21 of the 131 newly introduced orphan medicines can be attributed to the Regulation. This means that without the EU Regulation 110 orphan medicines would have been introduced. The impact of 21 represents almost 20% extra on top of the 110.

the average lead time (based on 70 products that actually reached the EU market) was 30 months (Table 20).

A similar analysis for orphan medicines with market entry after 2000 shows that for this group the difference between market entry in US and EEA was on average 1 month. The difference in lead time between the two groups would thus indicate a substantial reduction of 29 months in the time to market since 2000.

However, this difference cannot be wholly attributed to the EU Orphan Regulation. Analysis of the development in the lead time for non-orphan medicines in the same time period shows that this lead time has decreased by approximately 11 months between 1990-2000 and 2010-2018, or by almost 70%. This general trend in access is likely to have applied also to the orphan medicines and orphan-likes. Correcting for this general trend, **the isolated impact of the EU Orphan Regulation on the lead time to market for orphan medicines in the EU is assessed at a reduction of 9 months**¹⁴³.

Table 20 Time to market introduction in EU for various types of medicines

	Average time between International product launch data and marketing authorisation date	Number of EU12 member states in which product is available after 3 years
Orphan-likes (before 2000)	30.2 months	3.7 Member States
Orphan medicines (after 2000)	1.1 months	5.7 Member States
Non-orphan medicines (before 2000)	15.9 months	2.9 Member States
Non-orphan medicines (after 2000)	5.2 months	4.2 Member States

Source: own analysis IQVIA database.

Wider availability of orphan medicines in the EU

A similar analysis has been carried out to assess the impact of the Regulation on the spread of *availability*. Availability is herein measured by the number of EU Member States where orphan medicines are available three years after central marketing authorisation. This analysis was carried out for the EU12 only to have a consistent basis for comparison over time, as the EU internal market expanded over time with various enlargements to the EU28.

As shown in Table 20, after three years, orphan-likes were on the market in 3.7 of the EU12 markets, while orphan medicines were generally available in 5.7 EU12 markets (or 54%). Correction for market trends was applied by reviewing also the availability of non-orphan medicines over time. This showed an increase of 1.3 Member States (44%). Correcting for this trend, we arrive at an estimated

¹⁴³ The impact has been calculated as follows: 30.2 (lead time orphan-likes before 2000) x 5.2/15.9 (reduction lead time non-orphan medicines between the years before 2000 and the years after 2000, reflecting the market trend) – 1.1(lead time orphan medicines after 200) = 8.8 months (effective impact on lead time to market for orphan medicines).

0.34 additional Member States of EU12 (or 3% of the EU12 population) attributable to the EU Orphan Regulation.¹⁴⁴

This impact was subsequently extrapolated to EU28 level by taking into account population and overall availability of orphan medicines in the other 16 Member States. Based on this corrected and extrapolated result, we conclude that, **three years after central marketing authorisation, orphan medicines are additionally available to 2.7% of EU population (or 14 million citizens) as a result of the EU Orphan Regulation.**¹⁴⁵ As shown in section 6.2.1, markets become more mature over time, implying that this impact may further grow after these three years.

Summarising the analyses, the estimated impact of the EU Orphan Regulation is assessed to be:

- The development of 18 to 24 new orphan medicines that would not be available otherwise;
- The faster introduction of orphan medicines in the EU, by on average 9 months per orphan medicine;
- Orphan medicines are marketed in more EU28 Member States, meaning that they become additionally available to 2.7% of EU population (or 14 million citizens) within the first three years following the marketing authorisation.

The impact described above has been used as input for the analysis of costs and benefits in 8.3.3.

Impact of business strategy on accessibility of orphan medicines

An element that is hard to quantify, is the extent to which the EU Orphan Regulation has affected marketing decisions by companies that operate globally, i.e. companies that potentially have the opportunity to vary the timing and the jurisdiction in which to launch new products. Based on more qualitative information from stakeholders, it is clear that for pharmaceutical companies the possibility of exclusivity in the EU is considered an important component, even if other jurisdictions also offer useful incentives and pathways.

Additionally, the framework of the Regulation is considered important, as it allows companies to know what data are needed to achieve marketing authorisation, which in turn informs their global development plans. Knowledge about the speed and certainty of access in a particular Member State can help

¹⁴⁴ The impact has been calculated as follows: 5.7 (number of Member States in which orphan medicines are available) - 3.7 (idem, for orphan-likes before 2000) \times $4.2 / 2.9$ (general market trend as reflected in the development of availability of non-orphan medicines over time, before and after 2000) = 0.34 .

¹⁴⁵ The exact calculation is as follows: population of the EU16 was around 25% of total population of EU28 at 1.1.2017. Based on IQVIA-database the availability of orphan medicines in EU16 is calculated to be 65% of the level of EU12 (in 2016). The additional spread in EU16 is thus calculated to be: 3% (share of population EU12) (population) \times 65% (availability of orphan medicines) = 1.95% . The total impact for EU28 is estimated to be $75\% * 3\%$ (EU12) + $25% * 1.95\% = 2.7\%$ (EU28).

businesses come to a decision more quickly as regards the business case for launching an orphan medicine in a specific Member State.

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7.4. Impact on medicinal products for treatment of rare diseases in children

Where the question of unmet medical need perhaps most visibly comes into play is in the extent to which children and adolescents are the targeted patient population. Although the EU Orphan Regulation is not specifically intended to increase paediatric drug development and contains no obligation for the development of drugs for a paediatric population, around two-thirds of rare diseases occur (also) in children (EURORDIS, 2005a).

The data presented in Section 5.4.5 already showed that 76% of all designations and **111 authorised products are for conditions that affect (also) children**. However, **of these 111 products 50% (56) have so far been approved for paediatric use**. Our findings are supported by a recent study by Giannuzzi et al. (2017) which found that nearly half (46%) of orphan medicines targeting conditions that affect both children and adults had not been approved for paediatric use (as compared to 71% in the US).

It is unknown for how many products paediatric trials are still ongoing and for which a paediatric indication could still be added in future. The time-trend analysis shown in Figure 26 and discussed in Section 5.4.5 suggests the number of products with a paediatric use indication could still increase somewhat. It is also **not known for what share of products** paediatric investigations were completed but for which **the results did not justify addition of a paediatric use indication**. It can thus not be concluded that these developers have not (yet) made the required efforts to develop products for paediatric use.

Another study by Giannuzzi et al. (2017) researched why marketing authorisations for orphan medicines fail but did not explicitly note differences in the failure reasons for paediatric orphan medicines as opposed to other orphan medicines. The study, however, notes that **paediatric trials are often more challenging than other trials**, due to methodological, ethical and financial reasons, especially when neonates are involved.

Among surveyed developers of orphan medicines (n=18), 55% indicated having performed R&D on products intended primarily for use in children (regardless of

whether these products obtained a marketing authorisation). They did so mainly because it aligned with other in-house R&D activities (n=11, 33%), because they already had a product under development that was considered likely to offer significant benefit in children (n=7, 21%), or because they had specific experience and expertise in paediatric medicines development (n=6, 18%). Nearly half (14, 42%) of them indicated having never been involved in R&D for medicines primarily intended to treat children with rare diseases, with one respondent unaware of whether their company had been involved in this.

Developers were also asked about their **main reasons for not engaging in the development of orphan medicines for paediatric conditions**. Just over half of the respondents (n=8) stated that it is **not applicable in the therapeutic area(s) in which they are active**, as they focus on conditions that do not affect children. This, however, does not explain why also for conditions that affect both adults and children paediatric development is often slow or absent. Other reasons, such as insufficient expected financial return on investment, or the complexity of conducting clinical trials in paediatric populations were only mentioned by individual respondents. One respondent had been involved in paediatric development also indicated that paediatric development is often delayed due to uncertainty about toxicity in children. Overall, this rather small sample size does not provide a conclusive view on the reasons for insufficient development of paediatric orphan medicines.

Following the introduction of the EU Orphan Regulation, in 2007 the EU Paediatric Regulation was introduced to improve the development of high quality and ethically researched medicines for children through the establishment of Paediatric Investigation Plans (PIPs). A 2014 study assessed all designated orphan medicines, their indication, marketing authorisations, paediatric investigation plans and indication group (adult or child) (Kreeftmeijer-vegter, Boer, & Vlugt-meijer, 2014). The outcome and duration of the process from orphan drug designation to marketing authorisation, was compared per indication, and by age group to assess the effect of the Paediatric Regulation on the application process. The study concluded that **the Paediatric Regulation did not result in an increase in the number of orphan designations with potential paediatric indications**. It was also associated with a longer time to marketing authorisation for both adult and paediatric orphan indications. Nonetheless, it contributed to further paediatric development of medicines for which paediatric use otherwise could have remained off-label.

The **unmet medical need is felt particularly for paediatric oncological conditions**. The data in Section 5.4.5 showed that, of 38 authorised products for forms of cancer that affect (also) children, only 3 are for forms of cancer that are exclusive to this sub-population. Moreover, only 15 of these products were at one time approved for use in children. Similarly, a recent study found that between 2000 and 2016, 41% of oncological orphan medicines concerned a malignant condition occurring both in adults and children, but only 26% of authorised oncological orphan medicines had information for paediatric use in their SmPC at the time of the first marketing authorisation (Vassal et al., 2017). Even in subsequent updates to the SmPC post-authorisation, paediatric information was rarely provided. Only two orphan medicines had been authorised for a malignancy occurring specifically in children. The study

concluded that the EU Orphan Regulation has failed to promote the development of treatments for rare cancers in children.

These findings indicate that the focus of developers of oncological orphan medicines has been mainly on treatments on forms of cancer that (primarily) affect adults. One interviewee indeed suggested that developers do not look at paediatric cancers as rare diseases by themselves. The interviewee suggested that instead developers focus on rare cancers where the paediatric indication can be an extension of the adult indication. The paediatric indication is then added only after the development for the adult indication is completed. No data was collected directly from sponsors that would allow this statement to be verified.

Our data (Section 5.4.5, Figure 25) confirm that **paediatric development is somewhat less likely (or slower) to occur for oncological conditions than for non-oncological conditions¹⁴⁶ where there are both adult and paediatric populations**. The difference is, at least in relative terms, less pronounced than suggested by some representatives of patient and advocacy organisations and by participants in the online public consultation (both from health care professionals and individuals with personal experience with rare diseases) who singled out paediatric oncology as a field in need of particular attention. Possibly, this relates to the fact that – in absolute terms – there is a higher number of oncological products for which paediatric development has lagged. The fact that, compared to most other conditions, the patient community for paediatric cancers is larger and more organised, and therefore more vocal in its advocacy, may also play a role in public perception of this issue. Nonetheless, the interplay between the orphan and paediatric regulations poses some particular challenges with implications for paediatric oncology, as discussed further in Section 9.1.2.

7.5. Impact on landscape of R&D for rare diseases in Europe

The EU Orphan Regulation also aims to provide incentives for industry to develop and market orphan medicinal products and to encourage innovation. To achieve these aims, the Regulation would need to have an impact on the R&D landscape for rare diseases in Europe. In this section, we therefore look at the impact of the Regulation on the R&D landscape for rare diseases in Europe. We have made a distinction between the impact on the research environment (Section 7.6.1) and impact on the competitiveness of the pharmaceutical industry in Europe (Section 7.6.2).

7.5.1. Impact on research environment

It was already shown in Section 5.9 that, alongside the EU Orphan Regulation, the EU has supported various initiatives aimed at supporting the environment in which research for rare diseases takes place. Alongside this, national initiatives taken by Member States exist. As there is coherence between these initiatives (See also Sections 9.4 and 9.5), it means that it is not possible to

¹⁴⁶ When comparing to the average over *all* non-oncological products. There are substantial variations within this group, with some product categories showing a greater degree of paediatric development and others a much lower degree. However, these differences cannot be interpreted with any statistical significance, as the sample sizes within these individual groups are too small.

directly attribute any observed impacts on the research environment only to the EU Orphan Regulation¹⁴⁷. Rather than attempting to quantify and attribute the impact of the EU Orphan Regulation, we have thus focused on assessing how the research environment has changed and sought out the perspectives and experiences of different sets of stakeholders within that environment.

This assessment considered several types of impact, such as:

- Relative contributions of the EU Orphan Regulation and other initiatives
- Intensity and direction of research
- Collaboration between stakeholders

The information contained in the following sections is based primarily on the results of surveys conducted among representatives of developers of orphan medicines, academic researchers and experts, patient and consumer organisations, and – to a lesser extent – national public authorities.

Contribution of the EU Orphan Regulation to rare disease research

As stated, the EU Orphan Regulation is only one instrument within a broader set of initiatives to promote research for rare diseases. To better understand what level of importance different stakeholders attribute to different (types of) initiatives, they were asked to identify **which factors have had the most significant impact on stimulating R&D for orphan medicines in the last 20 years**.

A majority of academic researchers and experts (n=27, 55%) accredited this to the European support for research (such as the EU Framework Programmes), alongside the impact of the EU Orphan Regulation (n=22, 45%). This perception was largely shared by representatives of patient and consumer organisations, though more credit was given here to the EU Orphan Regulation (n=7, 30%) compared to the EU supporting programmes (n=4, 36%) and to the US Orphan Drug Act (n=4, 36%). In open commentary, several respondents specified that **the European research support stimulated *collaboration* within the research community**, whereas **the EU Orphan Regulation increased the focus on rare diseases and supported pharmaceutical companies in pursuing R&D in this area**.

Respondents from all stakeholder groups also frequently recognised the importance of national initiatives to support R&D, and of research networks such as the ERNs described in Section 5.9.1.

Importantly, both in surveys and in interviews, stakeholders emphasised that it has not only been the increased amount of funding and attention for rare disease research that has been important, but that also **scientific advances have played a crucial role**.

¹⁴⁷ Frameworks to support rare disease research and development of orphan medicines outside of the EU, in particular the US Orphan Drug Act, are likely to also make significant contributions of which the effects can be felt within the EU.

Intensity and direction of research

To understand in what areas the impact of the EU Orphan Regulation on the research environment for rare diseases can be seen the most, stakeholders were asked to reflect on the intensity and direction of research, both within their own organisations (where applicable) and from a more general perspective.

The majority of **developers of orphan medicines** (N=39) indicated that the EU Orphan Regulation has contributed to **expansion of their orphan product pipeline** (n=25, 64%), and to an **overall increase of R&D investment in orphan medicines** (n=23, 59%). Some highlighted that the EU Orphan Regulation has strengthened commitment of companies/organisations that develop orphan medicinal products to find needed medicines. The Regulation was also said to have drawn greater attention of investors towards this area, thereby further increasing R&D investments.

Around a quarter of respondents (n=9, 23%) indicated having reallocated resources or refocused their activities to new therapeutic areas or conditions with a focus on rare diseases. Although the sample size is too small to establish whether this accurately reflects an industry trend, it suggests that the **growth in the field of research and development for orphan medicines has been mostly additive** to overall pharmaceutical R&D rather than that it has displaced resources from other areas.

The increased intensity of, and spending on, research for rare diseases was also seen in academia. Two-thirds of academic researchers and experts (n=32, 67%) agreed that the Regulation had contributed to an increase in the overall intensity of research for rare diseases in the European academic community. Some also noted though that these effects cannot be easily measured. Nearly half (n=21, 44%) of these respondents also observed a shift in the focus of research into other therapeutic areas or methods as a result of the Regulation.

Whilst **patient and consumer organisations** are not usually directly involved in research for rare diseases and development of orphan medicines (aside from their obvious and crucial participation in clinical trials), all surveyed representatives (N=10) **agree, or even strongly agree, that the EU Orphan Regulation has contributed to an increase in the overall R&D efforts made to support the development of orphan medicines.** This opinion was held also by a large majority of representatives of **national public authorities** (n=29, 78%). Moreover, in this latter group of stakeholders, most (n=20, 59%) indicated that **the overall environment for developing orphan medicines had improved in their countries as a result of the EU Orphan Regulation.**

The here presented stakeholder perspectives only offer a qualitative assessment but they do not provide insight into impacts on the level of research activity in terms of scientific outputs (e.g. journal publications), or the number of clinical trials conducted. Some literature exists from the US on the impacts of the US Orphan Drug Act on research activity in the field of rare diseases. One study examined publications related to a cohort of rare diseases before and after the ODA was enacted (1976–2007) and found that the rise in publications was not statistically different from the rise in scientific publications overall during that

period, suggesting an inconclusive role for the legislation in stimulating rare disease research worldwide (H.E. Heemstra et al., 2009). Another study looked at the impact of the ODA on new clinical trials and found a 69% net increase in the annual rate of new clinical trials for medicines addressing rare diseases (Yin, 2008). Similar analyses were not included in this study for the EU Orphan Regulation, as these were considered out of scope.

Stakeholder collaboration

The EU Orphan Regulation also had an impact not only on the level of research for rare diseases, but also on how that research is done in terms of interactions with other stakeholders in the field. Many (n=24, 62%) developers of orphan medicines reported an increase in interactions with other organisations active in R&D for rare diseases. Additionally, a substantial share credited the EU Orphan Regulation with having contributed to increased interactions with patient organisations to inform and improve drug development (n=19, 46%), and increased engagement with patients (n=16, 39%).

Researchers, in turn, were asked how the Regulation had affected their collaboration with pharmaceutical companies, patient organisations, researchers in other disciplines. Many had experienced an increase in collaboration with patients, patient organisations and/or consumer organisations (n=17, 37%), with other researchers in the same discipline (n=16, 35%), and with pharmaceutical SMEs (n=12, 26%).

7.5.2. Impact on competitiveness of pharmaceutical industry in Europe

To better understand the impact the EU Orphan Regulation has had on the type of actors that are involved in R&D for treatment of rare diseases, an analysis was conducted of the sponsors of orphan designated products.

As discussed in Section 4.2.2.4, under the EU Orphan Regulation eligibility for orphan designation can be determined even on the basis of pre-clinical data (unlike, for instance, in Japan). This means that initial sponsors can comparatively often be parties other than large, experienced pharmaceutical companies. Sponsors of EU designated products include for instance academic researchers but also charitable foundations that engage in research. However, late stage clinical development is often exponentially costlier and thus often beyond the resources of small institutes or companies. In addition, the successful marketing and launch of a product requires specialized skills and expertise. Therefore, it is expected that, through transfer of orphan designations, the share of large pharmaceutical companies among sponsors increases as products come closer to a possible marketing authorisation.

The data presented in Section 5.7 and presented in Figure 27 show that **SMEs and pharmaceutical companies are sponsors of around 40% of all designations**. Smaller entities, such as academic institutions account for only a small percentage. **Marketing authorisations are held exclusively by pharmaceutical companies and registered SMEs¹⁴⁸**. The share of SMEs

¹⁴⁸ The here used classification by company type, however, does not take into consideration whether these companies perform any R&D or obtain product licenses through in-licensing or acquisition of other companies.

among sponsors has been growing rapidly (Figure 28). It is not known, though, to what extent this growth reflects an increased level of R&D activity (either overall or refocused on rare diseases) among SMEs, an increased maturity of their product pipelines, or simply greater familiarity with the ability to register as an SME with the EMA. The substantial share of consultancies (10% overall) listed as sponsors is somewhat surprising and raises questions about their role, as they are unlikely to be directly engaged in the R&D process. It is likely that they act as intermediaries for companies that are not established in the EU/EEA and thus in actuality represent the interests of another type of sponsor. No data was available that would provide insight into this.

Transfer of designations from one sponsor to another is relatively common. These transfers usually happen from smaller to larger entities, reflecting the reality that the resource needs increase exponentially in later stages of product development.

Around half of all sponsors are headquartered in the EU/EEA, and another third originate from the US (Section 5.7,

Figure 29). A much larger share (31 out of 33) of respondents to the survey for developers indicated performing at least some R&D activities in the EU/EEA, though it was not specified if this includes R&D on orphan medicines. **Transfer of designations has no appreciable net impact on the share of designations held by EU/EEA based entities** (Section 5.7, **Table 10**)

Various stakeholders have pointed out that the EU Orphan Regulation was not designed to improve the competitiveness of European industry per se compared to that in other parts of the world. Whilst it requires a sponsor to be established in the EU/EEA, there is no requirement that R&D activities are conducted there. In interviews, **developers suggested that where their R&D for orphan medicines is performed, primarily depends on factors such as a favourable economic climate, labour market conditions and the ability to efficiently conduct clinical trials, for instance because of the presence of centres of expertise.**

7.6. Maintenance, revoking and withdrawal of orphan designation

Only a relatively small percentage of all designated orphan medicines will eventually make it to the point of marketing authorisation, either because the product does not show the desired effectiveness in clinical trials, because the product is not sufficiently safe, or simply because the sponsor decided to not pursue further product development for commercial reasons. Even for those products that successfully make it through to the point of obtaining a marketing authorisation, however, not all will retain the coveted orphan designation and enjoy the benefits that come with that status. This has been further elaborated in the sections below.

7.6.1. Maintenance of orphan designation at authorisation

As detailed in Section 4.5.1, under the EU Orphan Regulation, the orphan designation is reassessed by the COMP prior to marketing authorisation. **Only if the product is found to still meet all the criteria for orphan designation, is able to sufficiently demonstrate significant benefit if necessary and is not found to be similar to a designated orphan product**

that is still protected by the orphan market exclusivity, the designation is maintained.

In interviews, COMP members have clarified that, whereas at the initial designation stage, the COMP can accept more limited evidence, in order to encourage even early stage development, at the time of assessment to recommend maintenance of orphan designation, sufficient data needs to be presented to demonstrate the medicine fulfils the criteria. If the COMP issues a positive opinion and the orphan status is maintained, the sponsor can commence to benefit from the 10-year market exclusivity reward for EU designated orphan medicines. Should the COMP recommend against maintenance of the orphan designation, the sponsor is no longer eligible for the orphan market exclusivity upon marketing authorisation.

7.6.2. *Withdrawal of orphan designation prior to or after authorisation*

A sponsor can voluntarily withdraw a product from the community register of orphan medicinal products and thus forego the rewards that come with the orphan designation. There are various reasons why a sponsor could opt to do so. For one, the orphan market exclusivity reward is incompatible with the 6-month paediatric extension of the supplementary protection certificate that was introduced as part of the Paediatric Regulation¹⁴⁹. Therefore, if the financial reward to be gained from the paediatric SPC extension is expected to outweigh that of the orphan market exclusivity reward, the sponsor may decide to give up the latter. Whilst this was not explicitly stated anywhere, various stakeholders believe this to be the reason for why Novartis withdrew its remaining orphan designations on Glivec, allowing it to obtain a paediatric extension (discussed also in Section 9.1.2).

Another possible reason relates to the fact that, as discussed in Section 4.5.3, under the EU Orphan Regulation it is not possible to have a single marketing authorisation for both orphan and non-orphan indications on the same product. Having to apply for and maintain separate marketing authorisations for the same product, and sustain two separate brand names, can be costly and cumbersome. Therefore, if there is insufficient financial benefit to be gained from the orphan market exclusivity, a sponsor may opt to remove the orphan indication from the register and instead maintain a single marketing authorisation. Whilst this issue was raised by some sponsors in the targeted consultation activities (interviews and survey responses), no data were offered that this particular aspect of the EU Orphan Regulation had slowed down, or even blocked, the possible development of a product for use in orphan indications.

7.6.3. *Revoking orphan designation after authorisation*

In theory, the EU Orphan Regulation allows for an orphan designation to be revoked after the authorisation if a product no longer meets the

¹⁴⁹ Section 29 of Regulation No 1901/2006 states “for orphan medicinal products, instead of an extension of the supplementary protection certificate, the ten-year period of orphan market exclusivity should be extended to twelve years if the requirement for data on use in the paediatric population is fully met.”

criteria. The mandate of the COMP to grant or withhold orphan designation is largely limited to the initial designation prior to marketing authorisation, and the reassessment for maintenance of designation at the time of marketing authorisation. However, Regulation 141/2000 contains a clause, Article 8(2), that allows the period of market exclusivity to be reduced to six years if, after five years on the market, the orphan criteria are no longer met (European Parliament, 2000). Triggering of this article is not automatic and the COMP does not conduct a routine 'audit' of all products in, or close to, the fifth year of the market exclusivity to establish whether the criteria are still met. Rather, **any request for such a reassessment needs to be triggered by at least one EU member state and the evidentiary burden to demonstrate reasonable doubt about continued eligibility falls on the requesting member state.** The sponsors are under no obligation to routinely submit data.

The clause appears to have been originally intended to prevent companies from making excessive profits from market exclusivity (Blankart & Stargardt, 2010). As noted in Section 3.3.1, **the wording of this article in the Regulation as it was adopted deviates from that in the original proposal in a way that, at the surface, may seem trivial but that has important implications for its effectiveness.** Under the current wording, the reassessment can only be triggered if the *original grounds* on which designation was sought for the product are no longer believed to be fulfilled (Commission of the European Communities, 2008b). This means that, for any product for which orphan designation was sought on the basis of the prevalence criterion, the designation can only be challenged if there are sufficient data to support that the prevalence of the orphan indication of the product exceeds the threshold.

Thus, **the designation cannot be challenged on the grounds of product profitability, if the designation was not sought on the criterion of expectation of 'insufficient return on investment'.** However, even if a designation would be granted on the grounds of this criterion, it is unclear how a Member State could request the reassessment as it has not been defined what constitutes "sufficiently profitable". In a 2005 report to the Commission, the COMP recommended that further guidance be given on "the criterion of insufficient return on investment and on the definition of "sufficiently profitable" to review market exclusivity at 5 years. This may imply amending the current Commission Regulation (EC) N° 847/2000 of 27 April 2000 (medical plausibility, criterion of insufficient return on investment) and the Commission Communication of July 2003 (market exclusivity, sufficient profitability)." (European Medicines Agency, 2006)

In response to this recommendation, the Commission commissioned a study offering considerations on the application of article 8.2 (De Varax, Lettelier, & Bortlein, 2004). This study outlined several possibilities for how the profitability of an orphan medicine could be evaluated, but also cautioned that the possibility of curbing the reward could act as a disincentive to invest in orphan medicine development. The report indicates that guidelines should be proposed before August 2006. This study could not confirm whether guidelines with respect to the definition of «sufficiently profitable» have since been provided. However, since no designations have been granted on this criterion, it is unclear what purpose this guidance would serve.

Placing the burden of proof on the Member States and imposing a narrow timeframe within which the request for reassessment can be issued, severely limits the possibility for Member States to trigger the review of the market exclusivity under Article 8(2). Survey results among representatives of national public authorities show that, whilst there is broad familiarity with the Article (28 respondents (74%) indicate being familiar), only three participating Member States had ever internally explored the possibility to invoke it, and only once did this result in a formal request.

In 2016, the UK requested a reassessment for the product *Plenadren*. Plenadren received an orphan designation for the treatment of adrenal insufficiency in adults. In response, the COMP reassessed whether the designation still met the prevalence criterion. Based on updated information provided by the sponsor and discussions with the COMP, it concluded that, whilst the prevalence had increased to 4.85 people in 10,000, this remained within the allowable limits. As all other criteria also remained fulfilled, the COMP concluded that the period of market exclusivity should not be reduced.

In a discussion with representatives of the Member States¹⁵⁰, there was a strong sense that **the responsibility to request a reassessment should belong to the EMA and COMP rather than to the individual Member States**. It was suggested that these have the resources and information needed to determine if prevalence estimates need to be revised in light of available information. This sentiment was also visible in the survey responses from representatives of national public authorities. These captured frustration with the fact that **it is virtually impossible to trigger the procedure, even if products are extremely profitable**. This frustration with the wording and interpretation of the Article 8(2) was shared by representatives of patient organisations. They view the article as **the strongest possible means to limit excessive profit making in theory but observe that, in practice, the article has been rendered useless**.

7.7. Concluding remarks on effectiveness of the EU Orphan Regulation

In this section, we summarise the main findings against the applicable evaluation questions, highlighting where questions remain.

Uptake and effectiveness of incentives

The various incentives all contribute to the development of new treatments for rare diseases. **The effectiveness of incentives varies**, based on factors such as the experience of the developer, market and product characteristics (e.g. need to demonstrate significant benefit), the stage of development of the product and various other factors (e.g. the existence of other intellectual property or regulatory protections). However, 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.

¹⁵⁰ Meeting of the Pharmaceutical Committee of 1 April 2019

Effectiveness in addressing unmet needs

Since the introduction of the EU Orphan Regulation, nearly 2000 products have been granted orphan designation and the number of authorised treatments has significantly increased. Between 2000 and 2017, 142 new orphan medicines were authorised for the EU market, compared to a baseline of somewhere between 15 and 70 treatments for rare diseases before the Regulation went into effect.

These new products cover nearly all main therapeutic areas, offering treatment options for a substantially greater range of conditions than was available before the Regulation was introduced. They thereby make a **useful contribution to addressing the hitherto unmet needs of patients with rare diseases**, including many very rare conditions. However, **in terms of bringing treatments to market in areas where none existed before, the Regulation is showing a diminishing rate of return.**

Whilst authorised products cover a wide range of areas and indications, a certain clustering can be observed, particularly around oncological treatments. This has been associated with a number of factors, including availability of scientific leads, alignment with existing R&D portfolio's, and the availability of other treatment options. Notwithstanding these legitimate explanations, it is likely not coincidental that clustering is seen primarily in areas that are also considered more lucrative.

There is an increasing tendency to grant conditional access to products with the promise of addressing areas of great need, but for which the evidence base is not yet sufficiently developed. The real value of such products to patients remains to be seen.

Overall, **the EU Orphan Regulation has contributed to addressing some of the unmet needs for patients with rare conditions, but the unmet need remains considerable.** It is unclear if, within the design of the EU regulatory framework for orphan medicines, greater outputs could have been realised with greater inputs. Access to the incentives offered by the Regulation is not 'capped': there is no limit on the number of developers or on the number of products that can receive the incentives offered by the Regulation, provided they meet the eligibility criteria. It is only within the incentives themselves that there are restrictions, most importantly the 10-year period of market exclusivity. As will be shown in Section 8.3, our analyses do not provide sufficient grounds to assume that a longer period of protection would have substantially increased the number of authorised orphan medicines on the market today.

Further acceleration of the development of orphan medicines may instead require an additional set of measures, either within or outside of this regulatory framework. A full exploration of alternative, potentially more effective and/or efficient, models to incentivise development of orphan medicines was beyond the scope of this study. However, the literature offers some suggestions and examples. A 2014 study, for instance, proposed the use of a 'megafund', issuing 'research-backed obligations' to de-risk orphan

medicine development and improve the expected rate of return (Fagnan, Gromatzky, Stein, Fernandez, & Lo, 2014).¹⁵¹

In the Netherlands, the Dutch government is backing the Fair Medicine Foundation, a non-profit foundation that brings together different stakeholders with the aim to develop new effective and affordable medicines, including orphan medicines¹⁵². However, these models thus far are unproven still. Within the area of product development for poverty-related and neglected diseases – which is similarly characterised by limited potential for return on investment – the model of product development partnerships has become popular¹⁵³. These non-profit organisations bring together actors from the public, private, academic, and philanthropic sectors to develop new treatments that are accessible and affordable to people in low- and middle-income countries. This model is being tested for some rare diseases as well, such as in the EspeRare partnership for XLHED, a rare genetic disorder.¹⁵⁴

At the level of access to authorised treatments, some improvements have happened under the EU Orphan Regulation: **across the EU, more products are available to patients with rare diseases, these products are being marketed in a greater number of countries and the time to launch has, on average, decreased.** However, in terms of the number of products available and the speed with which these become available, substantial variations exist between Member States. These variations are such that **in some countries patients can hardly feel the impacts of the Regulation at all.** Here, virtually all needs for treatment remain unmet. As discussed in the previous chapter, the EU Orphan Regulation does not contain the tools required to address these ‘downstream’ access issues.

Impact on orphan medicines for paediatric use

Since the start of the EU Orphan Regulation, 111 medicines have been brought to market for orphan conditions affecting children. This includes 14 products for paediatric-only conditions, whereas the majority are for conditions affecting both adults and children. Of the latter group, less than half have been approved for use in **paediatric populations.** Whilst this number could still increase, as more data are collected, so far only 56 orphan medicines are approved for use in children. This is disappointingly low given that 50% of all rare diseases already manifest in childhood (EURORDIS, 2005b). It indicates that, overall,

¹⁵¹ The calculations of the effectiveness of such a fund, however, take into consideration the existence of orphan market exclusivities and thus would not remove the current public costs from the system. Moreover, the fund would channel funds from global capital markets and thus is offered as an alternative model for private investment, rather than for public investment.

¹⁵² <https://www.fairmedicine.eu/en/>

¹⁵³ For instance, the Dutch government operates a Product Development Partnership fund to support development of diagnostics, treatments and vaccines for diseases such as HIV, tuberculosis, malaria and neglected tropical diseases. <https://www.government.nl/topics/grant-programmes/pdp-fund-against-poverty-related-diseases-2015-2020>

¹⁵⁴ <https://evpa.eu.com/news/2018/esperare-gains-rights-to-relaunch-late-stage-development-for-a-rare-genetic-disease>

paediatric populations have been relatively underserved by the EU Orphan Regulation framework. There are several possible reasons for this.

First, development has insufficiently focussed on rare conditions that affect children, which sponsors attribute primarily to a lack of fit with their R&D portfolios. Secondly, developers have insufficiently prioritised paediatric clinical development when products have the potential to benefit this population group. Whereas the Paediatric Regulation was introduced with the aim of stimulating the latter aspect, neither the EU Orphan Regulation nor the Paediatric Regulation offer tools or incentives to steer development specifically towards conditions affecting children.

Although the lack of development for paediatric use is seen across therapeutic areas and indications, it is most clearly felt in the area of paediatric oncology. Here also the interplay between the EU Orphan Regulation and Paediatric Regulation plays a role, as discussed in Section 9.1.2.

Competitiveness of European pharmaceutical industry

Representatives from all consulted stakeholder groups widely credit the EU Orphan Regulation with having strengthened the climate for R&D for rare diseases. They highlight that there has been a marked increase in the number of actors in the field, both in academia and in industry. Research networks have been created and companies have increasingly collaborated with academia and patients in the development of orphan medicines. Many large pharmaceutical firms now have a portfolio of orphan products under development. As such, the climate has improved overall. However, the Regulation does not contain any provisions that require R&D to be conducted in the EU. In fact, sponsors have indicated that decision-making on where R&D activities are conducted depends largely on other factors, such as the ability to conduct clinical trials, the presence of research networks and availability of researchers, as well as economic R&D incentives (e.g. tax breaks).

Analysis of sponsors shows that pharmaceutical companies and SMEs hold the vast majority of all designations and all marketing authorisations for orphan medicines. Nonetheless, smaller players such as academic institutions also play a part. Their role is mostly commonly in the earlier stages of the development process. In the later stages, sponsorship is frequently transferred to larger players. Transfer of sponsorship happens in equal measure to and from companies that are based in the EU/EEA. There is thus no clear indication that EU/EEA-based companies play a more significant role in some parts of the ecosystem than in others.

As there is no requirement for R&D to be performed in the EU/EEA, the Regulation does not have the means to steer research and thus only can make an indirect contribution to the competitiveness of the European pharmaceutical industry. No information was analysed to quantify the size of this contribution on, for instance, the number of companies active in the EU/EEA, the magnitude of R&D expenditure on development of orphan medicines, or on levels of employment in the pharmaceutical and biotech industries.

Granting and revoking market exclusivity

Granting of market exclusivity is dependent on the assessment of the COMP, on whether the product still fulfils all the designation criteria at the time of marketing authorisation. Whereas the criteria are sufficiently explicit, sponsors sometimes struggle to meet these, particularly when demonstration of significant benefit is concerned.

Whether a sponsor of an orphan medicine receives the orphan market exclusivity reward upon marketing authorisation of the product depends on: 1) if the COMP recommends maintenance of the designation, 2) if the sponsor opts to maintain the designation.

For recommending the maintenance of orphan designation, the COMP requires stronger evidence that a product meets the designation criteria than at the initial designation stage. Sponsors indicate that they sometimes opt to withdraw their designation due to associated costs of maintaining separate marketing authorisations for orphan and non-orphan conditions.

As introduced in Section 3.3.1 and further discussed in Section 7.6.3, the Regulation contains a provision that would allow the market exclusivity to be reduced to 6 years in case the eligibility criteria are no longer fulfilled. However, in practice this has not happened. Only once did a Member State request a review of the eligibility, but this did not lead to a reduction of the market exclusivity. The lack of use of this provision, and consequently its effectiveness relates to how it has been formulated: reassessment can only be done on the basis of the original grounds of designation. Consequently, the market exclusivity period for a product designated on the basis of prevalence cannot be reduced on the basis of its realised profit.

A second reason for the fact the provision is seldom used is that the reassessment can only be requested by Member States. These do not generally have the resources and information needed to monitor whether a request for reassessment is reasonable. Representatives of Member States have therefore argued that the responsibility should be shifted to the EMA and COMP. It is clear that in its current form the Regulation is explicit, yet not very effective in providing the possibility to revoke market exclusivity after a product has been authorised.

8. Efficiency

The EU Better Regulation guidelines for evaluation offers the following guidance for assessing the **efficiency** of EU actions:

Efficiency

Efficiency analysis considers the relationship between the resources used by an intervention and the changes generated by the intervention (which may be positive or negative). Differences in the way an intervention is approached and conducted can have a significant influence on the effects, making it interesting to consider whether other choices (e.g. as demonstrated via different Member States) achieved the same benefits at less cost (or greater benefits at the same cost).

Source: Better Regulation Toolbox, #Tool 47.

Thus, the effectiveness of the EU Orphan Regulation can be derived from the relation between the observed effects (i.e. products designated and authorised, R&D activity, industry competitiveness) and the inputs. Inputs herein takes into account the financial resources required to implement the Regulation – including the value of the rewards – on the one hand, and the costs of development of orphan medicines on the other. Where possible, the benefits derived from the Regulation have also been quantified.

This Chapter presents the analysis of the efficiency and its results. In addition, some reflection is given on whether the EU Orphan Regulation has resulted in any unintended outcomes and impacts, and how – if at all – these could be reduced

8.1. Introduction

This Section of the report presents our assessment of the efficiency of the EU Orphan Regulation, both in terms of the relation between costs and benefits, and in terms of its operational efficiency. We set out the data and analyses needed to answer each of the following three evaluation questions:

- Are the costs borne by the individual stakeholder reasonable in relation to the benefits (for the specific group)?
- Is there a fair distribution of costs between the main actors?
- Could the objectives of the Orphan Regulation have been achieved differently, i.e. at lower costs?

To assess the first of these three evaluation questions, costs of individual stakeholder groups are compared to their benefits. In this assessment, the costs and benefits are those directly related to the results achieved under the EU Orphan Regulation, which have been described in Chapters 5 and 7.

It has been assessed to what extent each stakeholder group has incurred extra costs related to the EU Orphan Regulation and what extra benefits have been derived from it. The methodology used is that of a societal cost-benefit analysis (CBA). However, since the main benefits (health impacts), are not expressed in monetary terms, the analysis is strictly speaking not a CBA. Rather, it is similar

to a cost-utility analysis (CUA), as it is carried out at the level of individual medicines.¹⁵⁵

The analysis is essentially backward looking; societal costs and benefits relate to the years 2000 up to and including 2017.¹⁵⁶ The scope of the analysis is the EU28¹⁵⁷, so costs and benefits are assessed based on the actual availability of orphan medicines and realised sales in these markets only.¹⁵⁸ The evaluation has, as far as possible, been carried out in accordance with EU CBA guidelines.¹⁵⁹ The analysis is presented in Section 8.2.

Whereas Section 8.2 focuses on the costs and benefits over a longer period, Section 8.3 specifically focuses on the costs and benefits derived by sponsors on individual orphan medicines. This analysis is necessary to assess to what extent the compensation derived by sponsors is proportionate to the costs and risks involved.

The overview of societal costs and benefits is the starting point for answering the second evaluation question described above, which essentially explores whether there would have been ways to get the same or better outcomes at lower cost. Specific areas where inefficiencies are observed, or are considered likely, are discussed in Section 8.4.

Assessment of the efficiency of any EU Regulation also requires a consideration of the administrative burden that falls on all stakeholders as a consequence. This is the focus of the discussion in Section 8.5.

The chapter concludes with a summary of main findings (Section 8.6).

8.2. Societal cost-benefit analysis

This section provides the information necessary to understand the assumptions and values that were used to conduct the societal cost-benefit analysis. First, it presents the different stakeholder groups that have been considered in the

¹⁵⁵ A cost utility analysis (CUA) is an economic analysis in which the incremental cost of a programme is compared to the incremental health improvement. The health improvement is not expressed in monetary terms, but in terms of impact on the health situation of patients. This impact is measured in additional life years gained, taking into account the quality of life during those years.

¹⁵⁶ Costs and benefits for these years have been calculated at price level 2018 and have been discounted at 3% to the base year 2018. The analysis is described in detail in Appendix F.

¹⁵⁷ Although the EU28 did not exist during the whole period due to successive enlargements of the EU, the analysis has taken these 28 countries as the basis for the analysis *throughout* the period.

¹⁵⁸ As besides EU countries the IQVIA database only contains information Norway data reflecting EEA and EU28 are almost but not wholly identical. As described in Part A of this Appendix, IQVIA data does not include Cyprus, Malta and Denmark giving a coverage of 25 out of 28 Member States. Furthermore, for some of these Member States the data are not complete (i.e. for The Netherlands, Latvia, Greece, Estonia and Luxembourg). The analysis has not been corrected for these missing data.

¹⁵⁹ See for instance: European Commission, *Better Regulation Toolbox, Tool 52, Methods to Assess Costs and Benefits*. 2017; European Commission, *Guide to Cost-Benefit Analysis of Investment Projects*, December 2014.

analysis, and the respective types of costs and benefits that they can be expected to derive from the EU Orphan Regulation.

8.2.1. Stakeholder groups and types of costs and benefits

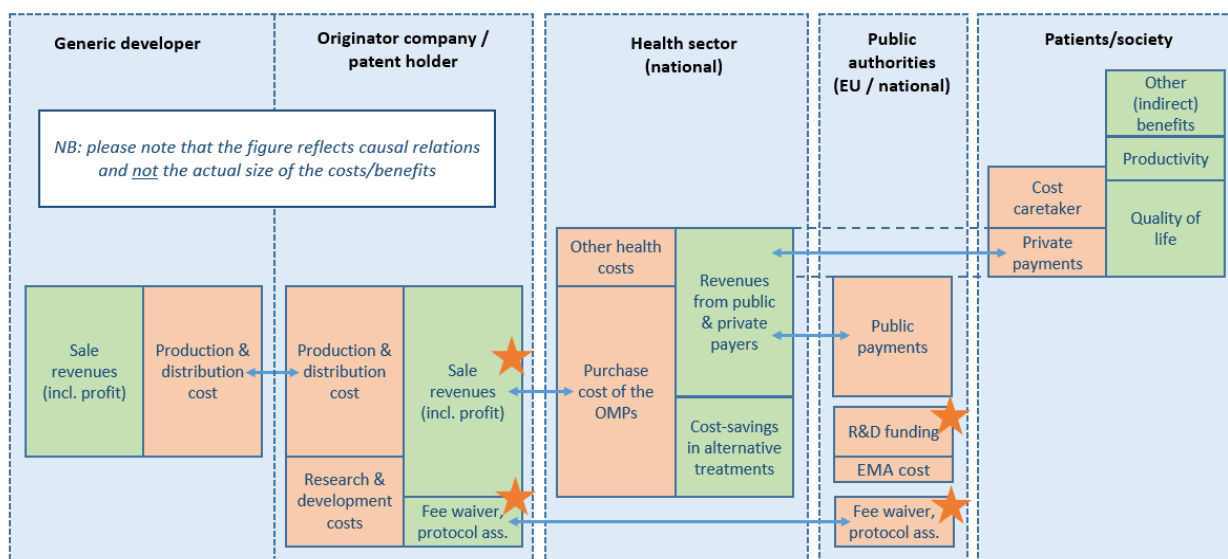
According to CBA guidelines¹⁵⁹, costs and benefits to society are assessed by comparing two situations: a situation *with* the policy/measure (in this case the EU Orphan Regulation) and the situation *without* the policy/measure. The latter situation is called the *counterfactual situation*, or, in case, such a situation cannot be established in accordance with the Better Regulation guidelines, the “*comparator situation*”. The results of the analyses that have been carried out to assess the impact of the EU Orphan Regulation, thereby defining the comparator situation, have been described in Section 7.3 and are the basis for the analysis presented hereafter. In summary, these impacts are:

- The EU Orphan Regulation is estimated to have contributed to the extra development of 21 orphan medicines in 2000-2017¹⁶⁰. This implies that 110 orphan medicines would likely have also been developed without the EU Orphan Regulation;
- Faster introduction: As a result of the EU Orphan Regulation orphan medicines were, on average, introduced 9 months earlier in the EU;
- Wider accessibility: As a result of the EU Orphan Regulation, a given orphan medicine is accessible for, on average, 2.7% of the EU28 population, or 14 million citizens, more than would have been the case without the regulation. For comparison, this equals the populations of Belgium and Lithuania together.

These impacts have resulted in both extra costs and extra benefits for a number of stakeholder groups. We have used the stakeholder groups and types of costs and benefits as defined in Figure 35.

¹⁶⁰ These numbers represent *aggregated* effects across the entire portfolio of products. It is not possible to identify specific products for which the EU Orphan Regulation can be said to have made a decisive difference. Rather, this should be interpreted to mean that the EU Orphan Regulation has played a role in the development decision for all products, but the extent of this may have varied from product to product.

Figure 35 Overview cost (red) and benefits (green) for various stakeholders



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 EU Orphan Regulation introduced (i.e. the market exclusivity, the protocol assistance, the fee waivers and the aid for research).

To better understand the analyses carried out and the results thereof, a few explaining remarks are in order, namely:

- For the **originator company or sponsor**, we distinguish two main cost components, i.e. (i) the research and development costs for orphan medicines and (ii) the costs of manufacturing, marketing and distribution of these orphan medicines, including a "normal" profit margin. In addition, the revenues from sales of orphan medicines and the three rewards of the EU Orphan Regulation, i.e. the market exclusivity (article 8 of the EU Orphan Regulation), the protocol assistance (article 6), and the fee waivers (article 7 sub 2) are regarded as benefits for the sponsors;
- The **developers of generic medicines** have no or only limited research and development costs.¹⁶¹ Their sales revenues need to cover (only) the costs of manufacturing, marketing and distribution, including a "normal" (industry average) profit margin. It is assumed that these costs are (at least in the long run) equal for both the originator and generic company, as they compete directly with each other (after the expiry of protection layers, like patents and market exclusivity). Developers of generic medicines do not incur the research and development costs for the reference orphan medicine;

¹⁶¹ It is recognised that this assumption is somewhat of an oversimplification. Demonstration of equivalence to the reference product will involve costs, though these are usually much smaller than those involved in development of innovative medicines. For biosimilar products, the R&D costs may be more substantial. However, since no biosimilar versions of any EU designated orphan medicines had been authorised at the time of analysis, these have not been considered in the analysis.

- The **health sector** is defined as comprising all medical services needed for the treatment of patients suffering from rare diseases. The costs of treatment with the orphan medicines, including the costs of the orphan medicines themselves, are regarded as costs which in first instance are borne by the health sector. These costs are **financed** from a combination of public and private sources. Public sources of financing are taxation or compulsory health insurance premiums. Private sources of financing are own contributions by patients (out-of-pocket expenses) and voluntary health insurance premiums. This financing is treated as revenues for the health sector;
- Public financing of the health sector is a major cost for **public authorities** (national governments, EU). Besides these costs, this group of stakeholders incurs additional costs related to the EU Orphan Regulation, such as administrative costs (e.g. the salaries of employees involved) and costs of providing the rewards;
- **Patients** incur costs in as far as they contribute to the financing of treatment with orphan medicines. Patients and others in society (such as their relatives, caretakers, employers) may also have additional costs or additional benefits resulting from the treatment with orphan medicines. The main benefit for this group is, of course, the health benefit derived from treatment with the orphan medicines.

Based on the impact of the Regulation, the extra costs and benefits have been assessed for each stakeholder group, using the above types of costs and benefits. In the following Sections, we present the results of this assessment. More details on the methodology (including any assumptions made), data sources used, and limitations are provided in Appendix F.

8.2.2. Cost and benefit estimates: pharmaceutical industry

As outlined in the previous Section, there are two main cost components for the pharmaceutical industry, namely:

- The cost of research and development for new orphan medicines
- The costs of manufacturing, marketing and distribution of orphan medicines that are being sold in the EU market.

These costs are specified further in the following paragraphs.

Costs of research and development

The industry incurs additional **R&D costs due to increased development of orphan medicines**. The cost of development of innovative medicines is a much-debated subject, as the industry has generally not been forthcoming with information on R&D expenditure at a product level. For this study, companies were asked by survey to provide estimates of their average annual R&D expenditure over the last five years on products that had potential application for the treatment of rare diseases. Only two companies provided any information (€26m and €160m respectively). Other respondents indicated that either this information was confidential or that such an estimate could not be provided since research is not always from the onset targeted at a particular disease.

Sponsors of authorised orphan medicines were also asked to estimate the total average R&D costs incurred per product by stage of the development process.¹⁶² None of the survey respondents were willing or able to disclose this information.

Anticipating a certain reluctance from companies to provide information on absolute expenditure on R&D on orphan medicines, an attempt was made to gain insight into the *relative* costs of development of orphan medicines. Hereto, companies that have both orphan and non-orphan authorised medicines in their portfolio were asked to estimate how the R&D costs of each of these types of products compared. Three respondents (21%) suggested that the costs of development of orphan medicines exceeded those of non-orphan medicines by a factor two or more, whilst three others estimated the costs as comparable or smaller. However, the majority of respondents indicated not knowing, or did not respond to this question at all. This lack of information and the large variation in the few answers provided means that this information could not be used in any meaningful way.

In interviews, industry stakeholders also repeatedly stressed that R&D costs should not be calculated at the product level, as they emphasise that such calculations do not account for failures. They also reiterated the point that it is not always clear *a priori* for what indication a product will be developed and whether this will be a rare disease. None of the interviewees provided any quantitative information on R&D costs for orphan medicines.

As these results from the consultation do not provide a sufficiently robust input for our analysis, we have instead used estimates of R&D costs for orphan medicines found in literature. Hereto two main publications are available:

- A study by the U.S. Department of Health and Human Services (U.S. Department of Health and Human Services, 2016) used the method of DiMasi (2016) to estimate the mean and median costs of development for orphan medicines. The authors estimate the mean costs of development to be US\$1.0b ((€725m¹⁶³) and the median costs of development to be US\$0.8b (€581m). The applied method of DiMasi takes into account the cost of capital used (for which in recent studies a real value of 11% has been used), as well as the costs of failures¹⁶⁴;
- Berdud et al. (Berdud, Drummond, & Towse, 2018) estimate the R&D costs of a new orphan medicine to be around US\$521m (€479m¹⁶⁵) for all indications and US\$493m (€453m) for oncology. They conclude that the estimated R&D costs for an orphan medicine is much lower (at round 27%) than the R&D costs for a non-orphan and that this is in line with other studies, such as that by Côté et al. (Côté & Keating, 2012).

¹⁶² For products authorised on the legal basis of Article 8(3) of Directive 2001/83/EC.

¹⁶³ Exchange rate per 31 December 2013: US\$1 = €0.7258.

¹⁶⁴ Based on the articles we assume that the presented costs do not take into account the subsidies provided from public funds towards the development of orphan medicines. For instance, DiMasi explicitly mentions that the focus is on private sector costs (see DiMasi, 2016).

¹⁶⁵ Exchange rate per 31 December 2015: 1 US\$ = €0.9189.

The **average R&D costs of orphan medicines mentioned are lower than the average R&D costs reported in the literature for other, non-orphan medicines**. This may be explained in large part by the much smaller numbers of patients involved in orphan medicine clinical trials and the shorter duration of those trials.

There are three aspects to consider that could increase or decrease the costs of development. First, some studies suggest that the type of orphan medicine may have an impact on the overall development costs (Schuhmacher, Gassmann, & Hinder, 2016). This applies for example to small molecules and biologicals, where, although biologicals are more complicated to produce, their development appears to be associated with higher chances of success.

A second aspect is related to the size and duration of the clinical trials before marketing authorisation, which may vary among orphan medicines. It has been observed that, in the EU, approximately 33% of authorised orphan medicines were tested in trials involving fewer than 100 patients, while more than 50% of the orphan medicines involved 100-200 patients in the trials. (Joppi et al., 2013) Also, for 43% of the orphan medicines, the clinical trials lasted less than one year. Another study found that clinical trials of orphan treatments are often limited by low patient numbers and poor follow-up (Winstone, Chadda, Ralston, & Sajosi, 2015).

Third, the issue of the cost of investment in R&D becomes particularly prominent in discussions with stakeholders relating to the subset of orphan medicines that are not new active substances, but are based on the **repurposing of established products** for which there was a **well-established use** prior to it obtaining an orphan designation.¹⁶⁶ This is because the costs a sponsor has had to make to repurpose or reposition a product may be substantially smaller than in cases where a sponsor has developed a wholly new medicinal product through all phases of the R&D pipeline, including the conduct of clinical trials (the issue has been discussed further also in section 8.4.2).

In our survey, developers of orphan medicines were asked to estimate the average costs associated with preparing the data dossier for orphan medicines authorised through a well-established use or hybrid application. However, none of the respondents provided meaningful quantitative information on this, with the majority indicating they had no such products. No data were found in literature that would allow us to estimate the costs to further develop established products for orphan indications. Therefore, a **separate cost-benefit analysis on such products was not possible**. Nonetheless, it is assumed that R&D costs for these types of products are substantially lower than the industry average for all orphan medicines.

¹⁶⁶ Repurposing is the process of identifying new uses for existing medicines in indications outside the scope of the original approved product information. For a discussion of repurposing please see 'Repurposing of established medicines / active substances,' Paper 8/37, prepared by the (European Commission) Expert Group on Safe and Timely Access to Medicines for Patients ("STAMP"), 8th December 2017.

Whilst the R&D needed to develop orphan medicines means that companies generate extra 'costs', these costs should not be allocated entirely to the EU/EEA market, as they will usually be covered also by sales in other markets. The Orphan Drug Report 2017 indicates that, in 2016, the global sales for orphan medicines were approximately €108b (US\$114b), with approximately €23.1b (US\$24.3b) for Europe (Hadjivasiliou, 2017).¹⁶⁷ This implies that 21% of worldwide revenues for orphan medicines are generated in Europe. For newly developed orphan medicines the sales outside the EU may be smaller than this division would suggest, in particular in the first few years after introduction, as marketing authorisations need to be realised. In this respect, it can be noted that the pharmaceutical sales in EU and US are similar¹⁶⁸, even though the EU population is about 50% larger than that of the US¹⁶⁹. Based solely on its share within the combined US and EU population size, thus excluding any other markets and not accounting for any differences in product accessibility or prescription behaviour, the EU could be argued to represent 60% of the total market, even though this is likely an overestimate. Our analysis thus takes a conservative approach by allocating 60% of R&D costs for orphan medicines to the EU market. In a sensitivity analysis, the effect of a smaller allocation has also been explored.

Using the above estimates and assumptions, the **EU Orphan Regulation is estimated to have led to an increase of €11.0b (discounted value 2018) in R&D expenditure for orphan medicines in the period 2000-2017**. This expenditure is borne as a cost by industry. A detailed explanation can be found in Appendix F, Section F5.3.

Costs of manufacturing, marketing and distribution of medicines

In addition to the R&D costs, producers incur **costs for manufacturing, marketing and distribution** of these medicines, including a "normal" (industry average) profit margin.¹⁷⁰ These costs have been assessed, using the results of an analysis of the economic value of the market protections, discussed further in section 8.3.2. This analysis showed that, on average, 30% of revenues from sales of orphan medicines can be regarded as the value of the market exclusivity reward, whereas, on average, 70% of revenues reflect the cost level of generic competitors. Based on the extra sales of €19.1b (see next paragraph), these

¹⁶⁷ EvaluatePharma uses a broader definition of orphan medicines than is used in this report. Their sample includes "all products that have orphan drug designations filed in the US, EU or Japan." Due to the difference in definitions, the sales data are not readily comparable.

¹⁶⁸ IFPMA reports overall sales of US\$312 b in the EU and of US\$316b in US for 2014. See: IFPMA, The Pharmaceutical Industry and Global Health, Facts and Figures 2017.

¹⁶⁹ As of July 2019, the reported population sizes were 513 million for the EU and 327 million for the US.

¹⁷⁰ The assessment of these costs, including a normal profit margin, is based on the methodology used to assess the economic value of the market exclusivity reward as explained in Appendix F, Section F4. In this analysis, it is assumed that the price level at which generic entry is profitable reflects a "normal profit" level, as this price is realised in competitive conditions. The size of this profit level, however, cannot be determined exactly and may differ per product.

costs **over the years 2000-2017 are assessed at €13.4b** (discounted value 2018).¹⁷¹

Revenues from increased sales of orphan medicines

The most obvious 'benefit' from the EU Orphan Regulation to developers of orphan medicines is that, in case they successfully bring a product to market, they will be able to generate additional sales in the EU/EEA. As such, development of a greater number of orphan medicines implies a greater total sales volume.¹⁷²

On top of this, as explained in section 7.3, producers benefit from the Regulation because their orphan medicines enter the EU/EEA market more quickly and because they are sold in more markets. All these factors contribute to increased sales revenues in the EU as a result of the Regulation.

All effects taken together have resulted in **increased sales of orphan medicines in the EU market in 2000-2017 of an estimated value of €19b**(discounted value).¹⁷³ Almost 45% of this is due to sales from newly developed orphan medicines, another 44% is due to faster access to EU/EAA market of the other 110 orphan medicines and 11% due to wider spread of medicines.

Revenues from market exclusivity reward

The 10-year market exclusivity for authorised orphan medicines potentially offers both an additional 'layer' of protection and an extension of the effective period of protection from competition by similar products. As the additional protection offered by market exclusivity may co-exist with (multiple) other forms of protection (for instance, when the market exclusivity period overlaps with the patent/SPC protection), its value could not be quantified. Only the impact of the longer duration of the protection could be taken into account. On average, the additional protection period resulting from the market exclusivity is 3.4 years, as elaborated in Section 5.6. **We estimate the value of this extension of the period of protection at €4.6b** (discounted value 2018).¹⁷⁴

Benefit from fee waiver and protocol assistance

Besides the extra revenues realised through additional sales, the pharmaceutical industry has also received rewards offered by the EU Orphan Regulation. The value of those rewards can be expressed in monetary terms. The value of the provision of the fee waiver and protocol assistance rewards

¹⁷¹ These costs represent 70% of the extra revenues realised by industry (i.e. 70% of €19.1b = €13.4b. See section F5.3 in Appendix F for more details.

¹⁷² This assumption, however, does not take into account that newly introduced orphan medicines may 'replace' existing ones if they can be used to treat the same population. In such cases, total sales and revenues could potentially decrease if the new product is marketed at a lower price than the original or if the dosing requirements are lower.

¹⁷³ See Section F5.3 in Appendix F for a detailed description on the various elements of these higher revenues.

¹⁷⁴ See Section F5.3 in Appendix F for more details.

under the EU Orphan Regulation during 2000-2017 is estimated at €0.2b (discounted value 2018).¹⁷⁴

Overview of costs and benefits for industry

Table 21 below summarises the discounted value of the costs and benefits for industry incurred in 2000-2017, based on the assessed impact of the EU Orphan Regulation and using average values for the inputs. It shows that the total net benefit for industry during 2000-2017 has been assessed to be slightly negative, at around -€0.5b. This does not mean that operations have been loss making for industry, as in both R&D costs and the costs of manufacturing a reward for capital already has been taken into account.¹⁷⁵ Rather, the net 'loss' implies that revenues are not sufficient to realise an additional return of 3% (the applied discount rate).¹⁷⁶ This calculated effect represents the 'costs' for industry as a whole, and does not account for the fact that variation may exist between companies with some operating on a substantially more profitable basis than others.

In interpreting this estimated net loss, it should also be kept in mind that, whilst the analysis includes the full costs of development for the 21 orphan medicines, it has compared these only to revenues generated in the period of analysis (2000-2017). The analysis, however, does not account for potential *future* revenues. Many of the included products have only been on the market for a relatively short period of time and can reasonably be expected to continue generating sales revenues for industry for many years after 2017.

As described, there is significant uncertainty on inputs used, implying a large uncertainty margin round this estimate. When extreme values for individual effects are combined, the result can be quite different, as indicated in Table 21.

We therefore conclude that it is uncertain whether the net balance for industry has been positive or negative. In Section 8.3, an analysis is presented of what this means for the level of compensation.

Table 21 Industry Costs and Benefits, due to the Orphan Regulation, 2000-2017 (discounted value 2018, prices 2018, in € billions)

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		€19.1b
Costs of manufacturing, marketing, distribution and normal profit margins relating to additional sales of orphan medicines in EU	-/- €13.4b	
Extra revenues due to market exclusivity reward		€4.6b

¹⁷⁵ The R&D costs include cost of capital at 11% (in real terms). In the manufacturing, marketing and distribution costs a "normal" (industry average) profit margin is included.

¹⁷⁶ To enable valuation of a stream of costs and benefits, which may not have been realised at the same time, these are both converted to their present day (2018) value. For this conversion, a so-called 'discount rate' is used which reflects time preference of economic agents. The applied discount rate here is 3 percent.

Cost saving due to protocol assistance and fee waivers		€0.2b
Total	-/- €24.4b	€23.9b
NET BENEFIT	-/- €0.5b	
Range Net Benefits (minimum – maximum) ^b	-/- €11b to +€11b	

a) The cost estimates for R&D are net of public funding. b) In the minimum scenario, the higher R&D costs are combined with high orphan medicine development and low compensation. In the maximum scenario opposite assumptions are used.

8.2.3. Cost and benefit estimates: (national) health systems

This section details the estimates of costs and benefits respectively, from the perspective of (national) health systems.

Costs for the health system

From the perspective of health systems, the main costs are those incurred from the additional *use* of orphan medicines. Meaning, the costs related to providing the medicines to patients living with rare diseases. Ideally, this analysis would also consider the broader costs associated with providing the treatment, such as those for diagnosis, monitoring and administration of the treatment. Conversely, the introduction of a new orphan medicine may reduce other health costs for patients with the indicated condition, by substituting for less effective or more costly treatments.

Direct impacts on health care costs are typically taken into account in Health Technology Assessment (HTA). Therefore, HTA reports are the prime source of cost and cost-saving impacts for the health system. Based on the public database of University of York Centre for Reviews and Dissemination¹⁷⁷ and a list of HTA reports supplied by EMA¹⁷⁸, HTA reports were identified for 32 orphan medicines. These contain, to some extent, information that has been used for the CUA (see Table 22 below. A full list of references can be found in Appendix F, Section F5.3).

The main inputs from HTA reports that can be used in a Cost Utility Analysis are:

- Costs of treatment with orphan medicine and cost savings for alternative (comparator) treatment, per patient (costs for the health system)
- The health impact of treatment with the orphan medicine, as compared to any alternative treatment, expressed in terms of quality adjusted life years (QALYs) (health benefit for the patient)

¹⁷⁷ See: <https://www.crd.york.ac.uk/CRDWeb/ResultsPage.asp>. For 21 orphan medicines reports have been found (in the CRD database) with some economic information, mostly from NICE (UK) and ZIN (Netherlands).

¹⁷⁸ The list received from EMA contains hyperlinks to HTA reports of NICE (UK), ZIN (Netherlands), G-BA, IQWiG (Germany), AOMiT (Poland) and HAS (Poland) for 87 orphan medicines. The reports of G-BA, IQWiG and HAS generally do not contain economic information, while large parts of the reports of AOMiT are redacted.

- The Incremental Cost Effectiveness Ratio (ICER), which expresses the amount of extra health care costs needed to realise each additional Quality-adjusted Life Year (QALY).¹⁷⁹

Table 22 Overview of HTA reports with economic information

Contents of reviewed HTA reports	No. of reports
Limited /no economic information	10
No information on cost effectiveness	8
Insufficient information given (e.g. ICER given, but no treatment cost)	5
Information on ICER and cost of treatment, but no health impact / patient	14
Information on ICER and health impact per patient (in QALY)	8
Information on ICER, health impact per patient and cost of treatment	5
Total	50

Source: own elaboration. ICER stands for 'Incremental Cost Effectiveness Ratio', which is the ratio of the change in the cost of a therapeutic intervention (i.e. use of the orphan medicine) compared to the alternative or current treatment.

Unfortunately, few HTA reports contained all of this information. As can be seen from Table 22, 32 reports were found that contain information on ICERs, but only a few of them disclose the additional underpinning information. As a result, the impact on additional costs of treatment with orphan medicines or cost-savings in the health care system could not be assessed. Therefore, the extra costs for the health care system have been assumed to be equal to the extra revenues realised by industry.

Revenues for the health system

The extra costs for the health systems resulting from the EU Orphan Regulation need to be recovered from public and private sources. It has been assumed in the analysis that such costs are fully covered, implying that costs and benefits for the health system are balanced. Effectively, this means that the cost estimates provided here are carried over to another set of stakeholders, including governments (in case of publicly funded health systems) and patients (e.g. through insurance premiums and when co-payments apply).

Overall, this results in the costs and benefits due to the EU Orphan Regulation for the health sector summarised in Table 23. The uncertainty on the various parameters also has impact on this estimate. Taking upper and lower values for

¹⁷⁹ An incremental cost-effectiveness ratio is a summary measure representing the economic value of an intervention, compared with an alternative (comparator). It is usually the main output or result of an economic evaluation. 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 vs the alternative. York Health Economics Consortium; 2016. <https://www.yhec.co.uk/glossary/incremental-cost-effectiveness-ratio-icer/>

the additional development of orphan medicines, the net additional health costs range from € 20b to € 27b.¹⁸⁰

Table 23 Costs and Benefits due to the EU Orphan Regulation for the health sector, 2000-2017 (discounted value 2018, prices 2018, € billions)

Effect	Costs	Benefits
Extra costs due to treatment with orphan medicines	-/- €23.7b	
Additional extra costs due to new treatment	NDA	
Savings in costs of alternative treatment		NDA
Public and private financing		€23.7b
TOTAL	-/-€23.7b	€23.7b
NET BENEFIT		€0.0b

NDA: No data available to assess the effect

8.2.4. Cost and benefit estimates: governments and public organisations

The stakeholder group here referred to as “governments and public organisations” contains various types of governmental organisations, including national governments, and public or semi-public bodies that finance the health system. Additionally, we have included the EMA (including the COMP) and the European Commission who, whilst not paying for the costs of treatments with orphan medicines, incur costs through the implementation and rewards of the EU Orphan Regulation.

This stakeholder group experienced various types of costs due to implementation of the EU Orphan Regulation. Some are directly related to the Orphan Regulation, while others are indirectly related to them e.g. the extra expenses for the health system.

Costs directly related to the rewards of the EU Orphan Regulation:

- **EMA/COMP costs:** these costs refer to the additional costs resulting from the tasks that EMA executes in relation to the EU Orphan Regulation, as well as the cost borne by the EEA member states and other organisations in relation to the meetings of the various committees discussing applications for orphan designations and marketing authorisations. Annual costs for EMA and national governments have been assessed based on the approximate number of staff (in full time equivalents) involved in the various activities relating to the EU Orphan Regulation.
- **Research subsidies:** the EU and various national governments have provided subsidies for research to stimulate the development of orphan medicines. These subsidies are seen as fully additional costs, which might not have been available without the EU Orphan Regulation. This is likely to be an overstatement, as some of these public R&D programmes can reasonably be expected to have been supporting research on rare diseases

¹⁸⁰ The assumptions behind the lower and upper estimates are described in Section F5.3 in Appendix F.

even if the EU Orphan Regulation had not been realised. However, with the very limited information that is available, it was not possible to assess the extent to which these additional R&D expenditures would have been incurred in that situation.

- **Fee waiver and protocol assistance:** this is an integral part of the support provided by the EMA in line with its mandate to implement the EU Orphan Regulation. The costs of this assistance, which are incurred by the EMA, are fully financed by the EU.

Costs relating to financing of the extra costs of the health sector

A large part of the additional health care costs is reimbursed from collective sources (either government budgets, collective health insurance systems or otherwise). Healthcare systems across the EU Member States are organised and financed in different ways.

Eurostat reports at regular intervals on healthcare expenditures and financing. For instance, the online publication *Healthcare expenditure and statistics* of March 2018¹⁸¹ presents the healthcare expenditures by financing scheme for all Member States (except Malta). It shows that household out-of-pocket payments are an important source of healthcare funding in many Member States, accounting for nearly 7% of total expenditures in France to almost 50% in Bulgaria (average: 21%).¹⁸² In addition, voluntary health insurance schemes are used in various Member States. Taking these two sources of financing together, the estimated private share in expenses can be calculated to range from 16% in Germany to 57% in Cyprus (the EU average being 27%). The remainder is financed from either government budget or compulsory insurance or savings schemes.

Survey responses provided by representatives of national public authorities, indicate that:

- In the very great majority of responding Member States (17 of 20, 85%), the reimbursement mechanism for orphan medicines is the same as for non-orphan products.
- In the majority of cases (15 out of 20, 75%), financing of orphan medicines occurs through a national health service. In a minority of cases (6 out of 20, 30%), financing is also partly derived from a health insurance system.
- None of the responding Member States has a separate fund for financing orphan medicines, nor is voluntary insurance involved.

¹⁸¹ European Commission, see: <https://ec.europa.eu/eurostat/statistics-explained/pdfscache/37773.pdf>.

¹⁸² The report describes the average division of health care costs between private and public payers. It shows substantial variation between the EU Member States in the division of healthcare expenditures between public and private payers. For orphan medicine related expenditure the division may, of course, be different, as this concerns marginal expenditures for, in some cases, very costly treatments.

- For six reporting Member States (30%), out-of-pocket payments are reported.

Based on the above, we conclude that only a small proportion of costs related to orphan medicines is financed from out-of-pocket expenses by patients, most likely less than 5% of the total.¹⁸³ This does not take away from the fact that, in some countries, out-of-pocket expenditure can be considerably higher than this average. It also does not consider how treatment costs other than those for the orphan medicines themselves are financed (e.g. if doctor's appointments and medical tests require co-payments).

For the CUA a 97%-3% division has been used between public and private financing. This results in the overview of costs for governments presented in Table 24, with no monetary benefits identified.

Table 24 Costs due to the EU Orphan Regulation for national governments and EU, 2000-2017 (discounted value 2018, prices 2018, € billions)

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

8.2.5. Cost and benefit estimates: Patients and society

The last stakeholder group considered in the analysis is formed by those directly (patients) and indirectly (e.g. carers, relatives) affected by rare diseases, and others in society (e.g. employers).

The respective cost and benefit items considered for this stakeholder group relate to:

- Private payments for health care costs
- Non-healthcare costs of a rare disease
- Health benefits due to treatment with orphan medicines.

Costs for patients and society

As indicated previously, in the here conducted analysis it is **assumed that, in the EU, the large majority (97%) of all health care costs that are directly due to treatment with orphan medicines (excluding associated costs of treatment) is financed from public sources.**

¹⁸³ The reason is as follows: in 30% of Member States out-of-pocket payments are a source of financing of costs of orphan medicines. On average, such payments cover 21% of costs of the health care system. The approximate share of private payments could thus be $30\% \times 21\% = 6\%$. As treatment with orphan medicines can be costly, it is very likely that private contributions are capped and are (well) below the average out-of-pocket expenditure, so less than 6%. For the present analysis a level of 50% is assumed, so $50\% \times 6\% = 3\%$.

Ideally, the analysis would account for the fact that the societal costs of a disease are wider than those borne by the health systems. Examples of non-healthcare costs of a disease are use of social services, costs of involvement of (professional or informal) carers outside the health system, and productivity losses resulting from unplanned absences from work or early retirement by patients (or caretakers). The level of the non-health care costs and the impact of the treatment with the orphan medicine on the level of such costs depends very much on (i) the type of disease (e.g. typical patient groups, severity of disease), (ii) the nature of the treatment (e.g. curative or chronic care), and (iii) the effectiveness of treatment with an orphan medicine for an individual patient as compared to the alternative treatment.

Problematically for this analysis, however, HTA reports normally do not provide information on the impacts beyond the health system. Therefore, any **wider societal impact could not be established at the level of the Regulation**. Whether or not such an effect can be found at the level of a specific orphan medicine very much depends on the situation (as described above).

Health benefits for patients

Health benefits concern the improvement in the quality of life of patients due to the treatment with orphan medicines. These benefits can be expressed in terms of the number of quality-adjusted life years (QALY)¹⁸⁴ gained by patients. There is much debate as to what extent such benefits can be expressed in monetary terms and, if so, what value should be applied. In practice, these debates take place at the national levels and countries value health benefits differently. Therefore, the here presented analysis does not seek to estimate the health impact gained at the level of the Regulation in monetary terms. Instead, the societal gain in QALYs has been estimated.

The level of health benefits has been assessed using information on the Incremental Cost-Effectiveness Ratio (ICER¹⁸⁵), from HTA reports. ICERs were available for 32 orphan medicines, of which 24 relate to orphan medicines that have not been withdrawn from the market and for which sales were recorded in the EU. The ICERs differ considerably across orphan medicines, ranging from €23,000 per QALY to €1m per QALY. **The average ICER for these 24 orphan medicines is €110,000 per QALY.**¹⁸⁶

¹⁸⁴ A QALY is 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 1 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. (<https://www.nice.org.uk/glossary?letter=q>). For more information on QALY see for instance: MacKillop & Sheard, 2018, Quantifying life: Understanding the history of Quality-Adjusted Life-Years (QALYs), Social Science and Medicine, volume 211

¹⁸⁵ The incremental cost-effectiveness ratio is the difference in the change in mean costs in the population of interest divided by the difference in the change in mean outcomes in the population of interest. (<https://www.nice.org.uk/Glossary?letter=I>) It is therefore a measure for the 'value for money' a medicine offers in comparison to other treatments.

¹⁸⁶ See section F5.3 for more details.

As not all orphan medicines are used to the same extent in all countries, annual sales revenues have been used to calculate a 'weighted average ICER' for the individual years 2008-2016; this results in a **weighted average ICER of €54,000**.¹⁸⁷ However, this number may be an underestimation, as the group of orphan medicines contains medicines that have multiple indications, including for non-rare diseases. Moreover, the calculated average ICER is predominantly based on UK data, which may not be representative for other EU Member States. Important differences can occur between Member States due to, among other things, differences in prices agreed with suppliers, differences in the cost of comparator treatment, and differences in labour costs. To account for the uncertainty of the applicable level of cost utility, the analysis applies a range for the average ICER of €54,000 (weighted) to €110,000 (unweighted).

The much lower value for the weighted average (compared to the unweighted average of €110,000) implies that, **while many orphan medicines were expected to deliver health improvements at high costs per QALY, those that are actually on the market and reimbursed are generally more cost-effective**. These findings are in line with a recent paper by Berdud, Drummond and Towse (2018). These authors estimate the average ICER for orphan medicines appraised in Scotland and the UK to be around £70,000, while the average ICER of (7) orphan drugs with positive recommendations was assessed to be around £45,000.

Based on a multiplication of the calculated ICERs (range €54,000 to €110,000) and the estimated extra health care costs presented above, **it is estimated that, as a result of the Regulation, 210,000 to 440,000 QALYs were gained**. Overall, this results in the following overview of costs and health benefits for the stakeholder group patients (Table 25):

Table 25 Costs and Benefits due to the Orphan Regulation for patients, 2000-2017 (discounted value in 2018; prices 2018, € billion)

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

NDA: No data available to assess this impact

8.2.6. Outcomes of societal costs and benefits of the EU Orphan Regulation

When combining the above overviews of costs and benefits by stakeholder, we reach the following combined overview of results for all stakeholders (Table 26).

¹⁸⁷ In the unweighted average ICER all orphan medicines get the same weight (i.e. given that it is the average for 24 products the weight is 1/24). In the calculation of the weighted average ICER, the weight differs per product in line with the sales turnover in the EU for that product. Thus, the ICER of a product with high sales revenues has a higher weight than the ICER of a product with low sales revenues. The share of these orphan medicines in total turnover of active orphan medicines ranges from 35-60% in these years, as reported in the IQVIA database.

As the costs and benefits for the health care sector are assumed to be balanced, this stakeholder group is not shown separately.

Table 26 Costs and benefits associated with the Orphan Regulation 2000-2017 (discounted value 2018, prices 2018, € billion)

Effect	Patients	Industry	Governments	TOTAL
COSTS				
Aid for research			-/- €1.1b	-/- €1.1b
Fee waiver, protocol assistance		+ €0.2b	-/- €0.2b	€0b
Administration			-/- €0.02b	-/- €0.02b
R&D costs new orphan medicines		-/- €11.0b		-/-€11.0b
Extra costs manufacturing, marketing, distribution orphan medicine		-/- €13.4b		-/- €13.4b
Additional impact on health costs	NDA		NDA	NDA
Extra health care cost financing	-/- €0.7b		-/- €23.0b	-/- €23.7b
BENEFITS				
Extra sales revenues		€23.7b		€23.7b
Change in non-health costs of disease	NDA		NDA	NDA
NET BENEFITS	-/- €0.7b	-/- €0.5b	-/- €24.3b	-/- €25.5b
ICER	€54,000 to €110,000			
Health impact	210,000 to 440,000 QALYs			
Net societal cost per QALY	€58,000 to €118,000			

NDA: No data available to assess this impact

The overview shows that the extra expenses by governments and patients on extra health care costs, as a result of the EU Orphan Regulation in 2000-2017, are estimated at €23.7b (Table 26). Total net costs to society are slightly higher, at €25.5b. The difference between these two numbers is caused by the net costs for industry (€0.5b) and the costs of the rewards of the EU Orphan Regulation (€1.3b).

Using the ICER range of €54,000 to €100,000, the extra health impact is estimated at 0.2-0.4 million QALYs to patients with rare diseases. This implies an average societal cost per QALY of between €58,000 and €118,000, which is slightly higher than the estimated ICER values.

Importantly, the here presented results relate to the period 2000-2017. However, as the orphan medicines are still available (and new orphan medicines have been registered since), the various costs and benefits will continue in the future. Even if no new orphan medicines were to receive a marketing authorisation in the EU, the costs and benefits for the health system,

government and patients would continue in the future, as would the compensation for R&D by industry. This implies that the future costs and benefits will be similar to that shown above, but may increase due to the growing number of orphan medicines used. New developments may also affect the (cost-)effectiveness of orphan medicines, thereby changing the ratio between total societal costs and the health impact.

It should be emphasised that some important elements of societal costs and benefits could not be assessed with reasonable levels of robustness. Moreover, various other factors could not be taken into account in quantitative terms. Table 27 gives an overview of these limiting factors and simplifying assumptions in the analysis.

Table 27 Assumptions and non-quantified factors and their impact on the result of the analysis

Factor / assumption	Impact on outcome of analysis
Supply-side efficiency gains for industry not taken into account	The assessment of both the development costs of new orphan medicines and production costs does not take into account that larger industries may realise efficiency gains due to scale. It also does not consider efficiency gains due to technological advancement (e.g. improvement of genome technology). This may lead to overestimation of the costs, as well as overestimation of the impact of the Regulation in terms of development of new orphan medicines.
Survivor bias in 'orphan-like' comparison group	The effect of the EU Orphan Regulation on the time to market and geographic spread may be estimated conservatively. The health impact may have been underestimated accordingly.
Additional protection from market exclusivity compared to patent	By only quantifying the effect of a longer protection period (i.e. 3.4 years), the economic value of the market reward may have been underestimated, as the additional (concurrent) protection of the market exclusivity from similar products is not taken into account. This implies that the benefit for industry may have been underestimated, as well as the societal cost per QALY.
Repurposed products not accounted for in the modelling	The analysis assumes that all new authorised orphan medicines were newly developed products, involving substantial R&D. In the case of marketing authorisation on the basis of well-established use or previously products for which no marketing authorisation had previously been obtained (e.g. hospital formulations), the costs and health impacts may be overstated.
The analysis is limited to 2000-2017	The medicines that are developed as a result of the Regulation will continue to generate health impact. An analysis for a longer time period may show higher revenues for industry, but also higher additional health care costs and a higher health impact. As the development costs are already fully taken, while health benefits continue after 2017, total societal costs per QALY could be overestimated.
Impact on health care costs restricted to use of orphan medicines	The effect on health costs may be smaller or larger, depending on the total costs of treatment and the saved costs of comparator treatment. This implies uncertainty on the additional health costs and the additional health impact
Indirect economic benefits and costs are not quantified	There may be more benefits to society than shown above, but also more costs to society. The net effect of this on societal cost per QALY is unknown.
Health care expenses and health impacts realised may have different timing	The health care expenses and the health care impact included in the HTA reports represent the long-term impact of use of orphan medicines. In case orphan medicines prolong life substantially, the expenses and impacts may extend well beyond the timeframe of the analysis. As both costs and impacts are discounted, this may have an impact on the result of the analysis, in particular when costs are made upfront and health impacts cover a long period, well beyond the period used in the analysis. Due to this there may be an overestimation of the health impact for some of the orphan medicines.

8.3. Level of compensation for industry

In Section 8.2.2 the overall costs and benefits for industry as a result of the EU Orphan Regulation were estimated for the years 2000-2017. However, this analysis does not by itself provide insight into compensation at the product level, as cost and benefits are restricted to the specified time period. To gain insight in this, an analysis was conducted at product level. The results of this analysis are presented here.

As noted throughout this report, the market exclusivity reward was introduced because of the expected low return on investment in orphan medicines. By extending the period during which sponsors of orphan medicines are protected from competition, more revenues may be generated and a higher return on investment could be achieved. The present analysis evaluates whether the market exclusivity indeed offers a 'sufficient' compensation to encourage investment in development of orphan medicines. 'Sufficient' can hereto be defined in either relative or absolute terms. In relative terms, a sufficient level could be one similar to that of other, non-orphan medicines. In absolute terms, it relates to the level at which the investment in R&D can be fully recovered within the product's lifespan.

The analysis presented in this section is based on the following analytical steps:

- **Market characteristics** of orphan medicines and non-orphan medicines are compared (Section 8.3.1)
- The **economic value** of the market exclusivity reward is calculated (Section 8.3.2)
- The **level of compensation** is discussed (Section 8.3.3).

This section concludes with a discussion of the role of competition, as the extent to which competition emerges has a direct impact on the compensation a marketing authorisation holder for an orphan medicine can expect to receive (Section 8.3.4).

8.3.1. Comparison of market characteristics for orphan and non-orphan medicines

In chapters 5, 6 and 7 characteristics on turnover for orphan medicines and non-orphan medicines, as well as the level of competition experienced by non-orphan medicines were presented. It was concluded that:

- The annual turnover of orphan medicines shows large variation: about 50% of orphan medicines have an annual turnover of €10m or less in 2008-16, while 14% of orphan medicines show annual turnover of €100m or more. Some orphan medicines even realised an average annual turnover in excess of €500m in this period. (Section 5.8)
- The duration of the market protection differs per orphan medicine and ranges between 0 and 10 years. The average effective protection is estimated to be 3.4 years. (Section 5.6)
- The annual turnover of newly introduced non-orphan medicines shows a similar pattern, but relatively more non-orphan medicines show a higher annual turnover. Average annual turnover of non-orphan medicines,

including unsuccessful non-orphan medicines, is around 50% higher than of orphan medicines. (Section 6.1)

- In 31% of the analysed products, non-orphan medicines experienced competition from generic products. The probability of generic entry increases with average annual turnover. (Section 6.1)

8.3.2. Economic value of the market exclusivity reward

As part of this study, the 'economic value' of the market exclusivity reward (Article 8 of the EU Orphan Regulation) was assessed, to establish whether there is a 'fair'¹⁸⁸ compensation for the investments made by developers. The assessment methodology is described in Section F4 of Appendix F.

The analysis is based on two principal assumptions.

- In case of generic entry, the price of branded and generic products is expected to converge, and a new equilibrium price is reached. The new equilibrium price¹⁸⁹ after the expiry of all forms of protection (patent and SPC protection, data exclusivity and market protection and market exclusivity for orphan medicinal products) is seen as the price level that is sufficient for both generic developers and originator companies to cover the cost for production and distribution, as well as a normal profit margin.
- The difference between this new equilibrium price and the initial price charged for the reference product can be seen as the compensation for R&D development costs.¹⁹⁰

The approach included assessments of the economic value of two categories of medicinal products:

- 16 individual EU authorised orphan medicines for which the market exclusivity had expired;
- 342 individual non-orphan medicines.

The following paragraphs respectively discuss each of these two groups of medicinal products.

Assessment of 16 orphan medicines with expired market exclusivity

A total of 16 orphan medicines was identified within the IQVIA-database for which (i) the period of market exclusivity had ended and (ii) there were at least two years of IQVIA-data available after the end of the exclusivity period (i.e. two years after 2015-Q3). For each of these 16 products the specific comparator

¹⁸⁸ It should be emphasised that 'fair' is a subjective term and that there is no set threshold of return on investment above which the compensation can objectively said to be 'unfair'.

¹⁸⁹ It is expected that, after the protection expiry, the originator price will drop to the level of the generic price. If this is not the case, we see the generic price as the new equilibrium price.

¹⁹⁰ The methodology used assumes that after entry of a generic competitor the market reaches a new equilibrium, in which there is no longer room for overcompensation. However, this is not necessarily the case, as prices may remain high compared to production costs, even after a single generic producer has entered the market; the two market participants may charge duopoly prices. This will be true particularly in small markets where the number of generic entrants can be expected to be low, as is often the case for orphan medicines.

situation was identified and (where possible) the economic value of the reward calculated.

By the end of 2015-Q3, eight products remained under patent protection, but for one of them the patent protection ended only somewhat later, in 2016. In 2016 in total nine products were thus free from patent or regulatory protection and, in theory, susceptible to generic competition or competition from similar products.

Despite this absence of protection, no generic entry was observed in five of these nine cases. This lack of generic entry may (among other reasons¹⁹¹) be related to the relatively low sales volumes of these products.¹⁹² In addition, one product was still under market exclusivity in the US, delaying potential maximum sales volumes at global level for market entrants (the US market exclusivity for this product ended in March 2017). Although this does not automatically preclude generic entry in the EU, such generic entry was still not visible in the period up to 2017-Q3. For the remaining four orphan medicines, including the orphan medicine with an expired patent protection in 2016, generic entry was observed. In three of these cases, average annual turnover of the orphan medicine was well above €10m; in one case below (Table 28). For all four products, it was possible to determine a new equilibrium price, based on the price realised by competitors.

Using the difference between the price realised in the past by developers of the orphan medicines and the calculated equilibrium price, the economic value of the market exclusivity reward was calculated for the four products with observed generic competition. These calculations result in various absolute (gross) values of the market exclusivity, ranging from €2.4m to €5.1b over the period 2008-2017-Q3. On average, **the economic value of the market exclusivity for the orphan medicines was thus assessed at, on average, 30% of total turnover** (range 12-54%).¹⁹³ This percentage covers all types of protection applicable in the years 2008 until 3rd quarter 2017, including the market exclusivity reward.

It is emphasised, however, that not all orphan medicines experience competition from generic entry as evidenced by the fact that generic competition was seen in fewer than half of the orphan medicines that were no longer under any protection. In particular when annual turnover is low, the level of market entry is also low. This means that the market exclusivity may not have an economic value for all orphan medicines. Conversely, for products with high turnover, the economic value of the market exclusivity may be higher.

¹⁹¹ No review was conducted to see whether any efforts were under way to develop and register such products.

¹⁹² During the data period, the average annual sales are respectively: €9m, €3m, €1m and €27m.

¹⁹³ For a more elaborate explanation of the value, please see part 4 of Appendix F. Please note that for the majority of the orphan medicines, multiple protection layers exist(ed), which means the estimated economic value should not be attributed in full to the market exclusivity but is also related to other protection layers.

Table 28 Competition for orphan medicines free from protection, 2015 Q3-2017 Q3, by level of average annual turnover

	< €10 million	€10-100 million	> €100 million
Orphan medicines without protection*	4	4	1
- with generic entry	1	2	1
- idem (%)	25%	50%	100%

Source: own analysis of IQVIA data. * the product that only had patent protection in the US is included, as well as the one product for which the EU patent expired in 2016.

Economic value of protection of non-orphan medicines

A similar analysis was carried out for branded, non-orphan medicines for which the patent and SPC protection ended in the period 2011-2014. This analysis included a much larger number of products (342). In 93 cases (27%) generic entry was seen in the two years following the expiration of the protection, in particular for products with higher turnover levels. Subsequently, the economic value of the protection was calculated for these 93 products using the same methodology as used for the orphan medicines. The results show that **the economic value of the protection for these 93 products is, on average, 41% of revenues in the period between 2008 and 2017-Q3.**¹⁹⁴ The somewhat higher level is the result of the somewhat larger price difference between branded and generic products.

Conclusion on competition and economic value of protection

From the above analyses comparing the results for orphan and non-orphan medicines, two conclusions emerge. First, it appears that the level of competition for orphan medicines in the first two years after expiration of the protection is not inherently lower than that for non-orphan medicines. Second, the economic value of the market exclusivity for orphan medicines is, on average, not higher than the average value of the patent/SPC and regulatory protections applicable to non-orphan medicines. So, even though the market exclusivity reward extends the period of protection for orphan medicines beyond that of other protections, it does not result in a higher average economic value.¹⁹⁵

8.3.3. Level of compensation for R&D investments

Having estimated the value of the market reward, this insight was used to determine the extent of the compensation. The EU Orphan Regulation does not explicitly determine when the compensation for R&D investments (i.e. the economic value of the exclusivity reward) is 'fair' or 'proportional', but it does indicate, in Article 8, that developers should have the "*prospect of obtaining a market exclusivity for a certain number of years during which part of the investment might be recovered*" (Commission of the European Communities,

¹⁹⁴ See Section F4 in Appendix F for more details on this analysis.

¹⁹⁵ As the market exclusivity reward prolongs the protection period, it gives the sponsor the possibility for a longer period in which to recover R&D costs. This may have a downward effect on the price difference before and after generic entry.

2000a, Article 8). This implies that the economic value of the exclusivity reward on the one hand, and the needed investments on the other hand, should be 'balanced'. The overarching question here is to what extent any 'overcompensation'¹⁹⁶ is observed for orphan medicines in comparison to non-orphan medicines.

To address this question, the available literature on the impact of authorised orphan medicines on a company's valuation and profitability was reviewed (Table 29). Additionally, data on product sales and revenues were compared to the costs of development.

There are several publications that determine, at a more aggregate level, to what extent differences (i.e. 'overcompensation') can be observed in the financial or monetary performance of orphan medicine developers and non-orphan developers. Hughes and Poletti-Hughes (2016) assessed whether companies with orphan medicine marketing authorisation are valued higher and are more profitable than companies which do not have an orphan medicine marketing authorisation. (Hughes & Poletti-Hughes, 2016) They conclude that "*publicly listed pharmaceutical companies that are orphan drug marketing authorisation holders are associated with higher market value and greater profits than companies not producing treatments for rare disease*".

Miller (2017) studied the effects of the announcement of a new orphan medicine designation by the FDA on investors and the financial markets. (Miller, 2017) The main conclusion is that an "*orphan designation appears to be successful at generating positive value for companies, as seen by the positive and significant average increases in stock price.*" More recently, Lo (2018) compared for the period 2000-2015 the financial performance of 39 publicly traded companies specialised in developing drugs for orphan diseases with the financial performance of the broader biopharmaceutical industry and overall stock market. (Lo & Thakor, 2018) This study showed that the group of companies with orphan medicines in their portfolio 'underperformed' in the early 2000s, but that their financial performance improved over time, especially in the period 2010 to 2015. It is noted that this group has a higher volatility than other indexes, but still outperforms, even on a risk-adjusted basis.

The level of compensation can be assessed by offsetting the costs for development and marketing of a product against the revenues generated from these products. The latter should take into account the relative size of the EU market as compared to other markets, the turnover realised in the EU, the number of years in which it is protected from competition, and the economic value of that protection during this period. Most of these variables are different for orphan medicines as compared to non-orphan medicines.

As discussed in Section 8.2.2, for lack of robust primary data, we elected to work with estimates produced by major studies published in the peer-reviewed academic literature for calculating the costs of development of orphan medicines. This literature provides two separate costs of development estimates

¹⁹⁶ Overcompensation is here understood as the situation where the compensation for the development and marketing of the orphan medicine (i.e. the value of the exclusivity reward) exceeds the investments, which can be determined as the net costs plus a reasonable profit.

(of €479 million and €725 million respectively). These estimates are lower than the R&D costs for non-orphan medicines that are cited in literature, which range from US\$0.6b to US\$2.6b.¹⁹⁷

Table 29 Overview of literature on cost of R&D for non-orphan medicines

Authors	Year	Type of medicine	R&D costs a)
Mestre-Ferrandiz et al.	2012	New developed regular medicine	US\$1.5b
DiMasi et al.	2016	New developed medicines (N=106)	US\$2.6b pre-approval US\$2.9b post-approval
US Department of Health and Human Services	2016	New medicines since 2003	US\$1.1b to US\$2.6b
Prasad and Mailankody	2017	Cancer medicines	US\$648m
Deloitte & Global Data	2017	Average cost to bring a medicine to the market	US\$2.2b
Tay-Teo et al.	2019	Cancer medicines	US\$794m (range, US\$2,827-US\$219m)

a: Based on information contained in the articles, it is assumed that the presented costs do not take into account any subsidies provided from public funds towards the development of orphan medicines.

In comparing these costs against the revenues, one needs to take into account that, once developed, a medicine (being orphan or non-orphan) can potentially be marketed worldwide and substantially more revenues can be realised to cover the R&D costs.

The IQVIA-database allows the determination of to determine the total sales revenues¹⁹⁸ of orphan medicines that were available on the EEA market for the period 2008-2016 (full years).¹⁹⁹ As indicated in Chapter 5, within the group of identified orphan medicines, there are large variations in annual sales revenues. The QuintilesIMS Institute²⁰⁰ reported a similar distribution for the US market (QuintilesIMS Institute, 2018): from the 450 US orphan products (in 2016), 300 products (67%) realised annual sales below \$17m (€16.1m²⁰¹). The top-50 products realised an average annual sale of \$637m (€605m), followed by \$125m (€119m) for products 51-100 and \$46m (€44m) for products 101-150.

¹⁹⁷ See Appendix F for an overview of studies on R&D costs.

¹⁹⁸ The IQVIA-database reports revenue data on a quarterly basis, based on 'list prices'.

¹⁹⁹ Our market data covers the period 2008-2016 in the EEA; due to licence restrictions for the IQVIA-database, similar market data was not accessible for the period 2000-2007 or for non-EEA markets. The database has some limitations. First, it does not cover Cyprus, Malta, Denmark, Iceland or Liechtenstein. Second, for some countries, it has partial information only (i.e. only retail turnover): the Netherlands, Latvia, Greece, Luxembourg and Estonia.

²⁰⁰ The QuintilesIMS Institute was renamed as the IQVIA Institute for Human Data Science in late 2018. However, it continues to carry out wide-ranging research and analysis based on non-identified patient-level data.

²⁰¹ Exchange rate per 31 December 2016: US\$1 = €0.950.

Several conclusions can be drawn from the analysis of the level of compensation:

- Although the revenue base for orphan medicines is restricted by the small number of patients, low annual turnover is not unique for orphan medicines. Similar turnover levels can be found for non-orphan products. Notwithstanding this, the average turnover found in the EU for newly developed non-orphan medicines is generally somewhat higher than for recently developed orphan medicines.
- The level of competition seen for orphan medicines is not substantially different from that for non-orphan medicines, but rather the level of competition relates to turn-over: for both types of products, the level of competition increases with turnover of the product.
- The costs of product development are generally lower for orphan medicines than for non-orphan products.
- Annual sales in the EU of €10m will not give sufficient profitability if R&D costs exceed €600m, even if the market exclusivity effectively provides a full 10-year extension of protection from competition by similar products.
- Some orphan medicines realise sales well above €100m per year. For these products, additional market exclusivity does not need to be (the full) 10 years to enable the developer to recover costs, in case R&D costs are at, or below, the average level of € 600m.

It is thus concluded that, **for most orphan medicines, in particular those with annual turnover below €50m and average R&D costs, the market exclusivity reward will help to increase profitability, without giving the sponsor an unbalanced or unfair compensation.**

Clearly, situations can arise in which the market exclusivity reward is not needed or does not need to be 10 years to allow a sponsor to achieve a 'fair' compensation. In particular, **orphan medicines with high sales turnover in the EU (above €100m, at present 14% of the orphan medicines being sold in the EU) would not need a 10-year market exclusivity reward to be commercially viable, provided the R&D costs are not much higher than the average estimates found in literature.**

8.3.4. The role of competition

The previously presented analysis has looked at the economic value of the market exclusivity reward, with an assumption that market exclusivity is the main barrier to entry of (generic) competition. It is furthermore assumed that such competition would naturally result in a decrease of the price on the reference product.²⁰² However, there are various reasons to assume that in the field of orphan medicines these assumptions are tenuous. First, available data indicate that **even after expiry of the market exclusivity, generic entry of orphan medicines is limited.** A recent study on the US market indicates that, for the 87 orphan medicines that lost their exclusivity rights (before January

²⁰² Within the context of regular pharmaceutical products, generic entry normally results in a significant price drop. The 2009 EC Sector Inquiry reported an average price drop of 40% two years after market protection expiry. Copenhagen Economics reports a price drop of approximately 50% following the entry of generics.

2017), generic competition was visible for only 36 products (40%) (Sarpawari, Beall, Abdurrob, He, & Kesselheim, 2018).²⁰³ Another study also found that, for medicines no longer protected by either an orphan designation or a patent, in just 56% of the cases generic or biosimilar competition emerged (QuintilesIMS Institute, 2018).

One possible reason for the lack of generic entry upon expiry of the market exclusivity in the EU could be that **other protections are still in effect**, either in the EU (patents, SPCs, or data exclusivity and market protection) or in the US. In fact, both aforementioned studies note that for a substantial number of products, protection by a patent or SPC exceeded the orphan market exclusivity (Sarpawari et al., 2018) (QuintilesIMS Institute, 2018). This is consistent with the analysis presented in Section 5.6. Nonetheless, the existence of further protections in one market need not exclude generic entry in another market (in particular the US) where these protections are no longer present.

To further assess this, a high-level analysis was performed on sales data for the EEA for the group of 84 products that classify as US 'orphan-likes'.²⁰⁴ The analysis resulted in the identification of 54 products with generic competition, which is 65% of the total group.²⁰⁵ In 90% of these cases the product was introduced in at least one national EEA market before the end date of the patent or SPC in the US. This shows that, **whilst the continued presence of other protections in other jurisdictions may be a contributing factor, it does not deter generic competition all together.**

A 2018 IQVIA report on the US Orphan Drug Act, attributes the lack of generic entry primarily to the fact that **the prospective return on investment for generic orphan medicines is too small.** The report notes that just over half (116 out of 217) products that were no longer covered by market exclusivity or a patent faced competition, even sometimes decades after (QuintilesIMS Institute, 2018).

There are various factors that affect the profit-making potential for generic orphan medicines and that inform the decision-making on whether and when to develop and launch generic products. Some stem from the complexity of the EU Orphan Regulation. For example, under the EU Orphan Regulation there can be an accumulation of market exclusivity periods, when a product receives an orphan designation for more than one indication. This can keep products protected under the orphan status for a long time. As an interviewee from the generics sector stated, this creates more unpredictability and uncertainty for generic companies in the market of orphan medicines than in the market for non-orphan medicines. **Uncertainty of when not only a product, but also**

²⁰³ For one third of the US orphan medicines, the market exclusivity lasted longer than the patents. For two thirds the patent protection was longer.

²⁰⁴ Medicines that received orphan authorisation in the US before 2000 and have been available in EU without orphan designation.

²⁰⁵ In interpreting this relatively high level of competition it needs to be taken into account that there is a survivor bias in the group orphan-likes: those orphan-likes that did not survive on the EU market in 2008 or later are not visible in the analysis. The group thus only includes those medicines that were successful in the longer run. The success may have attracted generic competition.

an indication, reaches the end of the market exclusivity period affects the development of generic products.

A related reason is that in some instances, although the active substance of an expired orphan medicine becomes available for generic production for a particular orphan indication, **the therapeutic indication might be too narrow to be of interest to the generic company** as the expected return on investment is low. This is especially the case when the generic company cannot apply for a marketing authorisation that is broader than the originator's defined therapeutic indication, when a newly developed orphan medicine receives a second market exclusivity on an overlapping therapeutic indication.

All developers of generics and biosimilars (n=8) who completed the survey indicated that the **complexity of development and/or manufacturing is a factor in deciding whether and when to develop a generic or biosimilar version of an orphan medicine**. In addition, presence of other competitors (88%), insufficient total market size (75%) and expected brand loyalty to the reference products (50%) were cited as key factors. While we have noted previously in Section 8.3.3 that the development costs for orphan medicines may be lower on average for non-orphan medicines, the underpinning technology may be intrinsically complex and hard to replicate without substantial investment in engineering and production. These additional requirements may be sufficient to create barriers to entry, when linked with poor economics or insufficient technological capability.

As shown in chapter 5, a substantial share of authorised orphan medicines are biological molecules and therefore competition for these depends on the development of biosimilars. **There are, however, various factors that complicate biosimilar development in general and for orphan medicines in particular**. First, whereas generic versions of small molecule medicines are assessed on chemical equivalency, the objective for biosimilar medicines is to match the quality attributes of the reference medicine as closely as possible. This can be challenging because manufacturers of reference products closely control the release of commercial supplies based on demand and therefore these products can be difficult to come by for would-be competitors (Dowlat, 2016).

Also, because many orphan medicines have high prices²⁰⁶, the cost of procuring a sufficient amount of the original medicine to develop and confirm a biosimilar can be enough to unfavourably tip the balance of costs and expected revenues for generic manufacturers. Furthermore, when additional clinical trials are needed to demonstrate equivalence to the reference product and safety, problems can arise with patient recruitment as many patients (from an already small pool of patients due to the nature of rare diseases) will already be on treatment with the reference products and may be reluctant to switch to an unknown product (Dowlat, 2016).

All of these factors can pose barriers to the development of biosimilar orphan medicines, both in terms of the speed of development and of the economic

²⁰⁶ A high price herein is not defined in an absolute sense and is not based on list prices. Rather, the cost of procuring the medicine in sufficient quantities for testing can be comparatively high in relation to the potential profits that can be made from marketing a biosimilar version of that product.

feasibility of doing so at all. Therefore, **it is expected that entry of biosimilars into the rare disease market will be gradual** (Dowlatabadi, 2016). This is confirmed by the fact that, to date, the EMA has authorised 52 biosimilar products but none of these reference designated orphan medicines (European Medicines Agency, n.d.).

Aside from whether generic products are produced and authorised in the first place, there is also the question of to what extent these become available in different markets. Survey respondents indicated that **the main factors in deciding when and where to launch generic products are the patient population with the designated orphan indication in a country (63%), the expected level of competition (50%) and national pricing systems (50%)**.

A final consideration should be given to the effect of generic competition for orphan medicines on price. As illustrated by our analyses presented in Section 8.3.2, generic entry is often slow to emerge. This also means that limited data exists. What is clear from literature is that **even upon generic entry for orphan medicines, prices can be slow to drop and the price reductions are smaller than expected** (Cole & Dusetzina, 2018). For instance, even after three generic versions of Glivec²⁰⁷ (imatinib) entered the market, the price of Glivec remained around the same level, whilst the generic versions were priced in a similar range (Cohen, 2018).

8.4. Potential inefficiencies and undesirable consequences

While the EU Orphan Regulation can be considered a success in many regards, such as in terms of stimulating the development of new treatments for rare diseases and improving access across the EU/EEA, this success has not come without a cost. In general, orphan medicines have become 'big business,' which has had an impact both on the type of players in the industry and on some of the behaviours displayed. The latter in particular has been subject to increasing criticism (Roos, Hyry, & Cox, 2010)(Patel, 2017).

The first commonly heard criticism relates to the **high prices of orphan medicines and their overall cost-effectiveness**. It is felt that orphan medicine developers are exploiting their monopoly position (obtained by market exclusivity and other protections, or as a result of general market failures), by charging what is perceived as exorbitant prices under the guise of value-based pricing (Hughes-Wilson, Palma, Schuurman, & Simoens, 2012). Orphan medicines frequently exceed cost-effectiveness thresholds in HTA processes due to associated lack of evidence regarding clinical benefit and high acquisition costs. With this in mind, it has been acknowledged that standard HTA methodologies need to be adapted to take into account the specificities of each orphan medicine (Drummond, Wilson, Kanavos, Ubel, & Rovira, 2007). Lowering the price of orphan medicines to achieve cost-effectiveness at standard thresholds is likely to create a commercially unviable situation for manufacturers. The issue of pricing and the risk of overcompensation was addressed also in our discussion in Section 8.3.

²⁰⁷ Glivec (imatinib), a medicine produced by Novartis, was authorised in the EU as an orphan medicine for the treatment of chronic myeloid leukaemia in 2001.

A second concern is that **the Regulation has encouraged pharmaceutical companies to “game” the system**. The following sections highlight some of the areas where accusations of such gaming have been made.

8.4.1. Indication stacking

Under the EU Orphan Regulation, a product can receive more than one orphan designation. Each new indication requires a separate clinical development programme, request for, and granting of a European marketing authorisation. This forms the basis of why such development for additional orphan indications is independently rewarded.

As demonstrated by the data presented in Section 5.4.2, in the EU there are currently 22 products on the market that have been authorised for two or more EU orphan designations and that thus are entitled to multiple periods of market exclusivity. In principle, the concept of a product being authorised for more than one indication is not problematic. In fact, it could be viewed as desirable in that it enables products to be developed faster and at lower cost. However, there are two main areas of contention. The first relates to pricing of such products. The second pertains to the role of market exclusivity in extending the period of protection for extended periods of time, sometimes referred to as 'evergreening'. Each of these areas is discussed separately, with some concluding reflections provided thereafter.

Pricing and profits on products with multiple indications

As noted, whilst further development of products is by itself to be encouraged, **questions have been raised as to whether development for subsequent indications should be entitled to the same level of reward as development for the first indication**. The reason for this is that, as the substance in question is already known, there may be no need to repeat some studies, bringing down the overall development costs (Hughes-Wilson et al., 2012).

As part of this study, developers of orphan medicines were asked via survey to provide estimates of the cost of development for subsequent indications for authorised orphan medicines. However, no respondent was willing or able to provide this information.

Many stakeholders from outside of industry, however, in interviews and discussions expressed their discontent over what they perceive as an imbalance between costs and rewards. They note that orphan medicines that have been authorised for multiple indications have a correspondingly larger patient base and thus (much) increased profit potential. This particularly applies when products have been authorised for both orphan and non-orphan indications (even when these are marketed under separate names).

For instance, *sildenafil* and *iloprost*, in addition to their orphan status for the treatment of pulmonary arterial hypertension (PAH), have also been authorised for non-orphan indications (Blankart, Stargardt, & Schreyögg, 2010). *Sildenafil* is sold also at different doses and prices under the brand name *Viagra*[®] for the treatment of erectile dysfunction. *Iloprost* is sold under the brand name *Ilomedin*[®] in an intravenous form for the treatment of Buerger's disease and under the brand name *Ventavis*[®] in inhaled form for the treatment of PAH. Both products had already received marketing authorisation for treatment of PAH

before their marketing authorisation for orphan indications (i.e. *Viagra*[®] in 1998 and *Ilomedin*[®] in 1992 in the EU) (Blankart et al., 2010). As both are successful products with substantial turn-overs, it stands to reason that the bulk of the total R&D costs, for both the orphan and non-orphan indications, is covered by the revenues on the non-orphan indication alone.

One might expect that, with an increasing patient base, products that are authorized for additional indications display a proportional drop in price. Instead, a 2014 publication by Picavet et al., citing various other sources, concludes that “orphan drugs with multiple orphan indications are associated with higher prices. These results suggest that the **combined prevalence is not a determining factor for price setting**. Indeed, previous research showed that orphan drug prices are determined based on the prevalence of the first indication. **Launch prices for the first indication are unlikely to be reviewed following approval in other indications.**”(Picavet, Morel, Cassiman, & Simoens, 2014)(Denis, Mergaert, Fostier, Cleemput, & Simoens, 2010c)(Genane, Marinoni, Ando, & Reinaud, 2013)

The discussion on whether and how to reward ‘indication stacking’ often runs hand in hand with concerns about a practice known as ‘salami slicing’. This refers to the creation of ‘artificial’ subsets (the slices) of a condition (the whole salami), and then basing the prevalence of a condition on the sub-type and sub-population.²⁰⁸ The aim of this is to obtain the incentives associated with the Regulation through these new subgroups. A 2009 study of products designated under the US Orphan Drug Act suggested that pharmaceutical companies develop medicines for sub-indications of common diseases to profit from the subsidies offered (Yin, 2009). However, this study also estimated that only about 10% of the clinical trials for sub-indications would have been conducted without such subsidies.

The previously mentioned 2017 study by Kesselheim et al. (section 5.10) looked at biomarker-defined subsets of common diseases (Kesselheim et al., 2017). This study found that, of all authorisations granted in the US between 2009 and 2015 to orphan medicines, 13 were for such biomarker-derived subsets. It also found that for these 13 medicines, the clinical development times were comparatively short: all received at least one other expedited FDA designation besides the Orphan Drug Act designation (Accelerated Approval, Priority Review, or Fast Track). The median time between the initiation of human clinical trials and the submission of the full trial results dossier to the FDA was 4.6 years. Although shorter development times imply also lower development costs, the study reported no significant price differences between biomarker and non-biomarker defined oncological medicines.

As discussed previously in Section 6.3.4, under the EU Orphan Regulation, orphan designation on the basis of subsets of a disease is granted only under strict conditions.

Impact of consecutive market exclusivity periods and ‘evergreening’

In many cases, development of a product for second and further indications takes place, at least in part, *after* the product has been authorised for the first

²⁰⁸ <https://www.christenseninstitute.org/blog/salami-slicing-precision-medicine-orphan-drug-act/>

indication. This means that, if the product received an authorisation for additional indications, these will trigger a period of market exclusivity that is not fully concurrent with the first period. In the extreme, this can extend the period during which a product is under market exclusivity for an additional 10 years with each indication. The concern expressed by many stakeholders here is that this will effectively keep any generic competition out of the market for long periods of time, and possibly indefinitely.

It should be noted though that, whilst overlapping or consecutive periods of market exclusivity can indeed deter generic entry, they cannot prevent generic entry all together as each exclusivity period is tied to a specific orphan indication. Therefore, 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 (provided no other protections are in effect). However, in the Summary of Product Characteristics (SmPC) the marketing authorisation holder of the generic product cannot refer to those orphan indications that remain under market exclusivity. In interviews and surveys, some sponsors have pointed out that it can be difficult to effectively enforce additional market exclusivities when physicians are allowed to prescribe off-label. Nonetheless, **several representatives of generic manufacturers participating in interviews and surveys identified the presence of additional orphan indications as a barrier to development of generic orphan medicines.**

Reflections on inefficiencies related to multiple indications

Whether the societal costs of granting additional exclusivity rights for subsequent indications – thereby potentially delaying generic entry for *all* indications – are proportional to the additional costs a sponsor has to make for the clinical development of the product cannot be conclusively stated in the absence of data on the incremental costs of R&D and the extent of off-label use. However, it is likely that there is substantial product-by-product variation based on, among other things, whether and when generic entry occurs and how costly further clinical development has been.

Various stakeholders have called for a revision of the EU Orphan Regulation wherein development for additional indications is no longer rewarded with a full 10-year period of market exclusivity. Rather, these stakeholders **suggested that this period be reduced for each subsequent indication, as this better reflects the reality of the increased potential for return on investment.** However, in the absence of additional quantitative data on relative costs of development, **it cannot be established what length of market exclusivity would then be reasonable to bring a more acceptable balance between the costs and rewards.**

It has also been suggested that, in considering eligibility for orphan designation, the cumulative prevalence for indications covered by the product is considered rather than the prevalence of each indication individually. The risk of such an approach is that it discourages sponsors from further developing an existing product, instead incentivising them to focus on developing products that deviate from the original just enough to not be considered the same product. This would be undesirable from a patient perspective as it introduces new development risks and could delay the

development of important new treatments. It is **impossible to establish the magnitude of this risk and predict the impact of changing to a cumulative prevalence criterion.**

As a final remark, it is worth emphasising that in practice the number of products that are authorised for multiple orphan indications in the EU²⁰⁹ is small. Moreover, in most of those cases, the periods of market exclusivity for each indication overlap to a very significant extent. Under current conditions, therefore, the overall 'inefficiency' presented by indication stacking is relatively small and begs the question of whether a system overhaul is warranted. However, advances in personalised medicine in particular could increase the risk of artificial sub-setting to gain additional rewards.

In that sense, **any measure to limit incentives for additional indications should be viewed as intended to 'future-proof' the Regulation rather than to address a major existing inefficiency.**

8.4.2. Well-established use products, known active substances and price increases

Another area where many stakeholders perceive the EU Orphan Regulation to produce undesirable effects is in **how it rewards orphan medicines that had been in well-established use as hospital or pharmacy preparations prior to their authorisation as orphan medicines** or which are repurposed medicines that were previously known.

The EU Orphan Regulation permits that a company pursuing standardised production of pharmaceutical-grade²¹⁰ versions of these compounds for treating a rare disease can receive orphan designation for their preparation (Hughes-Wilson et al., 2012). The rationale behind incentivising the registration of these products is that this enables regulators to better monitor the product's effectiveness, quality and safety. It also allows payers to set conditions on pricing and reimbursement.

Whilst public debate, and discussions with stakeholders, frequently focus on existing treatments that have been 'reinvented' as orphan medicines, this involves a relatively small share of orphan medicines. Section 5.5 shows that under the EU Orphan Regulation 6 products have been authorised on the legal basis of Article 10a of Directive No 2001/83/EC for products in well-established use²¹¹. Another 21 products were authorised as known active substances. The reason, however, that these products garner a disproportionate amount of

²⁰⁹ This analysis does not account for products with both orphan and non-orphan indications that have been marketed under separate marketing authorisations, as required under the EU Orphan Regulation. In the US, no such requirement exists. Therefore, the number of orphan medicines with multiple authorised indications, including non-orphan conditions, is higher. Much of the public debate on indication stacking appears to have been based on US data.

²¹⁰ A pharmaceutical-grade compound (PGC) is defined as any active or inactive drug, biologic or reagent, for which a chemical purity standard has been established by a recognised national or regional authority. In this instance, it refers to the industrialisation of locally produced formulations.

²¹¹ *Granupas* (para-aminosalicylic acid), *Ketoconazole HRA* (ketoconazole), *Orphacol* (cholic acid), *Peyona* (caffeine citrate), *SomaKit TOC* (edotretotide) and *Tepadina* (thiotepa).

scrutiny is because **the obtainment of a marketing authorisation as an orphan medicine often involves substantial increases in the price of the medicine**, which before had been available to patients at a much lower price.

A recent, high profile example of this was the authorisation of Chenodeoxycholic acid (CDCA), a treatment for the 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 treatment of CTX and as the designation criteria were fulfilled, the EMA granted an orphan designation to Leadiant, the new name of Sigma Tau (BioSpace, 2018). Not long after this, the company increased 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 the registration was made on the basis a literature review and two retrospective cohort studies (Sheldon, 2018).

Another example is *Firdapse* (amifampridine)²¹², a medicine used to treat the symptoms of Lambert-Eaton myasthenic syndrome, which was granted marketing authorisation as an orphan medicine in 2002. This branded product is a minor alteration of an unlicensed and low-price compound that had been available for several decades. However, the price requested for the new product was 50- to 70- fold greater than the price of the already available unlicensed formulation. The situation led to an open letter to the Prime Minister of the UK from a group of neurologists and paediatricians (Nicholl et al., 2010).

More recently, the medicine *Lutathera* (lutetium-octreotate), used as a treatment for patients with neuroendocrine tumours, attracted negative publicity. The medicine was first developed by researchers in the Dutch Erasmus medical centre in Rotterdam. Their spin-out company Biosynthema became the sole producer of the medicine. During this time, the medicine was available to patients as a hospital formulation. In 2010, Biosynthema was sold to Advanced Accelerator Applications (a French company), who sought and obtained marketing authorisation as an orphan medicine. Subsequently in 2018, Novartis purchased the company and increased the price of the drug from €4,000 to €23,000, making the medicine too costly for many payers to justify reimbursement (Hordijk, 2019).

Interestingly, both *Firdapse* and *Lutathera* were authorised as new active substances, despite being only a minor variation of an existing product (*Firdapse*) or one that had been in use for many years prior to the authorisation (*Lutathera*). This shows that the legal basis for the authorisation is itself not a very good indicator for the investments made by the party that is granted (or later obtains) the marketing authorisation.

Price increases such as these appear to be unrelated to actual costs of R&D as the development had already been completed many years before and the products were previously sold at a much lower price. Here, it is **likely that the**

²¹² <https://www.ema.europa.eu/en/medicines/human/EPAR/firdapse-previous-zenas#overview-Section>.

market exclusivity that the marketing authorisation holders gained from the orphan designation was the main factor that enabled them to engage in monopolistic price setting.

Reflections on inefficiencies related to well-established use products and known active substances

The fact that the current regulatory framework for the EU Orphan Regulation does not contain any provisions to safeguard the affordability and accessibility of orphan medicines even when no significant R&D investments have been made by the sponsor, can be seen as a significant inefficiency. Although the EU Orphan Regulation cannot exert influence over product pricing, various stakeholders have **suggested that at least the Regulation could differentiate rewards depending on the type of application for marketing authorisation or the level of investment in R&D.**

Applications such as those for well-established use products and known active substances should herein receive a smaller reward – that is, a shorter period of market exclusivity – than new active substances. However, similar to our discussion on development for multiple indications (Section 8.4.1), the absence of quantitative data on the costs of development for such products means that it is not possible to objectively estimate what constitutes an appropriate size of reward.

8.4.3. Concentration in commercially lucrative areas and indications

The data presented in Sections 5.4.1 and 5.4.2, and the discussion thereof in Section 7.2.2, highlights that development of orphan medicines has tended to cluster around certain therapeutic areas, and even specific indications. This clustering suggests that the Regulation is not sufficiently effective in steering R&D towards areas of greatest unmet medical need. It can simultaneously be viewed as an inefficiency in the system in that **public resources are being directed towards supporting the development of products of diminishing value to patients.** The tendency for clustering was observed already early on: based on an analysis of results of the first four years of application of the Orphan Regulation, which showed a significant concentration of orphan medicines in the areas of oncology and metabolic disorders (65% of products), it was suggested that **the Regulation provides an incentive for manufacturers to concentrate on lucrative areas** (Varax, Letellier, & Börtlein, 2004).

It should be noted that, in addition to profit potential, **there are factors that help to explain this clustering.** A key reason why there is a skew towards the approval of cancer treatments is that a high proportion of treatable rare diseases are rare cancers, in addition to the increasing prevalence of cancers - rare and otherwise – due to an ageing population (Kanavos & Nicod, 2012). More generally, product development tends to happen most in areas where there is good knowledge of disease aetiology and where there are promising scientific leads. In interviews, some stakeholders from industry have even touted clustering as an indicator of the success of the Regulation, as it shows that in these areas 'normal' market dynamics are being created, whereby patients have multiple treatment options and competition emerges.

It is important to recognise also that the requirement of demonstration of significant benefit means that, at least in the view of the COMP, each follow-on orphan medicine offers some measure of additional value to patients. Nonetheless, various stakeholders – particularly those representing payers – have raised the question of whether development of new orphan medicines in areas where there are already treatments available should be rewarded as much as more ground-breaking treatments. Here too it has been suggested **a more graded reward system is needed, with shorter periods of market exclusivity for each consecutive product for the same indication.** However, **insufficient data is available to offer suggestions on what could constitute an appropriate set of graded rewards.** Also, it is difficult to predict what the impact of this could be on the development of potentially highly relevant treatment alternatives, that could offer patients substantial clinical benefit or reduce healthcare costs.

As an alternative to a graded but fixed set of rewards, one could also consider **linking the period of market exclusivity to the level of therapeutic added value offered compared to existing treatments**²¹³. In theory, this offers the possibility of more strongly encouraging radical innovation compared to incremental innovation, and steering R&D towards areas of greatest unmet need. However, here too **the practical application of such a system will face difficulties.** First, there is currently **no single agreed approach to establish therapeutic added value.** In 2015, the European Parliament published a study that explored the possibility of introducing a harmonised EU assessment of the therapeutic added value of medicines (van Wilder, Valentina, Kuipers Cavaco, & McGuinn, 2015). This study offers policy recommendations for how this could be taken forward within the current legal framework. Indeed, such action is high on the political agenda in Europe: the third Joint Action for HTA focuses, among other things, on developing common assessment methodologies (The European Commission, 2018). Nonetheless, at the moment it appears unclear if and when the EU will adopt such a harmonised HTA approach.

A related complication would be the matter of **who would be responsible for determining such therapeutic added value.** In the case of authorised orphan medicines for which there is already a treatment option available, the COMP already assesses significant benefit. For the moment, however, the COMP assesses only if, and on what grounds, a product offers significant benefit, but it is not tasked with 'quantifying' that benefit. Whilst not impossible, requiring the COMP to do so would further add to their already substantial workload

²¹³ Revue Prescrire annually reviews all new products or indications. In 2018, it deemed that only 13 out of 99 new medicines offered 'a notable therapeutic advance', whereas 50 were judged to be 'nothing new' (<https://english.prescrire.org/en/81/168/57220/0/NewsDetails.aspx>. Accessed July 2019). The assessment of 'significant benefit' for orphan medicines means that it needs to be established that newly authorized products offer benefit over existing treatments where any exist. As such, it can be argued all orphan medicines offer therapeutic added value. However, the EU Orphan Regulation framework does not differentiate the market exclusivity period based on whether a product is 'first in class/therapeutic area' or an incremental improvement over existing treatments.

(discussed in the following Section) and would possibly require additional expertise.

A third important consideration is **how a graded reward system would impact innovation**. For instance, linking the reward to therapeutic added value means that a developer will not know what reward it can expect to receive until *after* the development is completed, or at least at a very advanced stage, as that is once clinical trial results are available. This introduces a great deal of uncertainty for developers and is likely to have a negative impact on any *ex ante* risk-benefit calculations made to inform pharmaceutical investment decisions. A similar argument applies to a reward system that differentiates between first-in-class and follow-on products based on order of authorisation. Due to the inherent unpredictability of research, a developer cannot anticipate if they will be first-to-market for a specific indication. In this way, the uncertainty of whether a product will make it to market at all, and gain market exclusivity, is compounded with the uncertainty of what reward it will receive if successful. These **uncertainties could mean that developers could opt to entirely forego development in areas where others are already active**. Pruning the pipeline this way could slow down innovation and eventually even result in no products coming to market at all for particular indications if remaining players are unsuccessful.

Another associated danger is that such graded systems will **further drive a “race for the line”**, as only the first to market will receive the full reward. This could encourage sponsors to reduce their time investment in clinical trials. As a result, products may come to market with a smaller than necessary evidence-base, complicating the task of regulators and HTA agencies and increasing the need for post-marketing data collection.

A final caveat to this suggestion would be that offering a shorter period of market exclusivity could mean that, to still maximise the return on investment during the protection time offered, sponsors would simply **charge higher prices**. As mentioned previously, many payers have shown a greater willingness-to-pay for orphan medicines than for non-orphan medicines, which may signal to sponsors that there is room for further price increases.

A more radical suggestion offered by some stakeholders is to **exclude specific therapeutic areas entirely from eligibility for orphan designation**. In particular, some suggested that all oncological products be excluded from consideration, as for those products the market appears to be sufficiently attractive even without additional incentives. The risk of such an approach is that **this may simultaneously remove incentives for development of products with a less favourable outlook on profitability for indications within that same therapeutic area**.

Reflections on inefficiencies related to clustering of indications

This study cannot offer specific recommendations on what precise measures to take to reduce system inefficiencies in a way that does not jeopardise some of the successes achieved by the Regulation. Each of the here presented alternatives has its benefits and risks but lacks substantiating evidence to adequately predict what the impacts thereof will be. Nonetheless, it is clear that **among those who pay the cost of orphan**

medicines there is an urgent call to reduce these perceived inefficiencies.

8.5. Administrative burden on stakeholders

The study has included consideration of the 'administrative burden' placed by the EU Orphan Regulation on various stakeholders. It reviews also whether the procedures involved in applying for, reviewing and granting of orphan designations are appropriately efficient. These procedures have been explained previously in Section 3.3.3.

This section draws primarily on information obtained by consultation of sponsors, representatives of the EMA and EC, and members of the COMP. The Better Regulation Guidelines for impact assessment and evaluation (Tool#53) require that the net administrative costs of information obligations imposed by an EU legislation are determined. Administrative costs should herein be defined as "the costs incurred by enterprises, the voluntary sector, public authorities and citizens in meeting *legal obligations* to provide information on their action or production, either to public authorities or to private parties." A distinction is made between so-called 'business-as-usual' costs which correspond to the costs an entity would have incurred even in the absence of the legislation and the administrative burden that stems from the part of the process which is done solely because of a legal obligation. The Better Regulation guidelines thus define 'administrative burden' as "those costs borne by businesses, citizens, civil society organizations and public authorities as a result of administrative activities performed to comply with information obligations included in legal rules".²¹⁴

Section 8.5.1 discusses applicable estimates of the administrative burden. Additionally, Section 8.5.2 offers up a more qualitative reflection on the administrative burden associated with the Regulation.

8.5.1. Estimation of administrative burden

In considering the administrative burden on stakeholders, three groups of stakeholders were here considered: developers of orphan medicines, the EMA, and public authorities in the Member States. Citizens and civil society organisations are not expected to bear any costs as a direct result of the Regulation, as they have no legal obligations with respect to the Regulation and are affected only as beneficiaries.

From the perspective of developers of orphan medicines, one should bear in mind that application for orphan designation under the EU Orphan Regulation is voluntary: developers remain free to develop and market any product intended for the treatment of rare diseases in the EU even without an orphan designation (provided they show a positive benefit-risk ratio and are authorised by a competent authority). Therefore, **the administrative burden imposed by the EU Orphan Regulation on developers is effectively zero.** This does not mean developers do not incur any costs as a result of the EU Orphan Regulation,

²¹⁴ Better Regulation Toolbox, Tool #58. Typology of costs and benefits. Available at https://ec.europa.eu/info/sites/info/files/file_import/better-regulation-toolbox-58_en_0.pdf, last accessed July 2019.

but simply that these costs are not obligatory. Our consultation did not seek out further quantitative information from product developers on such costs.

As it remains helpful to nonetheless understand what the administrative burden is that compliance with the requirements of the EU Orphan Regulation poses on sponsors of orphan designated products (e.g. the costs of applying for a designation, the requirement to submit annual sponsor reports, and the cost of collecting and providing the information required for demonstrating eligibility at the time of marketing authorisation), **sponsors were asked in qualitative terms about their experiences with the procedures involved and the administrative burden thereof.** This has been described in Section 8.5.2.

Estimates of the recurring costs involved with application of the EU Orphan Regulation by the EMA are offered in Section 8.2.4. This shows that **the costs for the administrative tasks performed by the EMA in relation to the Regulation are small compared to the costs of fee waivers and protocol assistance.**²¹⁵

Member States also incur costs that can be attributed directly to the EU Orphan Regulation, aside from those associated with the costs of treatment with orphan medicines. In accordance with Article 7(2), every year Member States pay a special contribution to the EMA to cover the costs of fee waivers. Alongside this mandatory contribution, Member States also contribute indirectly by nominating national experts as members to the COMP. These members are not reimbursed for their work in the COMP. The organisations from which they are seconded thus indirectly bear the costs as a result of time spent by COMP members outside these institutions. No estimates are available of these costs.

8.5.2. Stakeholder experiences with administrative burden

The following Sections discuss the administrative burden on stakeholders involved in various parts of the process, from initial application for orphan designation to the marketing authorisation stage, in a qualitative sense.

Application for orphan designation

Consulted sponsors and representatives of industry associations indicated that they **do not generally view the application process an administrative burden, as it is entirely voluntary** (unlike the requirement to file and complete a paediatric investigation plan mandated by the EU Paediatric Regulation). Some did note that the process is resource-intensive, though no cost estimates were given. No attempt was made to estimate how the costs of applying for an orphan designation in the EU compare to those in the US or Japan.

Among survey respondents, most sponsors (N=36) found the quantity and type of information required to support the initial application for an orphan designation, 'acceptable' (47%), 'good' (28%) or 'very good' (6%). **The application process itself was considered acceptable or better by all respondents with direct experience of this.** A similar level of satisfaction

²¹⁵ The administrative costs are based on the number of EMA staff dealing with orphan medicines, as well as the time input by national and EU representatives in the meetings of the COMP. We assessed the annual combined input at 15 -20 full time equivalents.

was expressed with the predictability of outcomes of the application process and clarity of the criteria for application. It was noted though that individual company experiences can vary and that companies that have previously been through the process are more likely to find the outcome of the assessment predictable. The predictability of outcomes also becomes less if other treatments are available (i.e. significant benefit needs to be demonstrated). Some sponsors specifically highlighted that there is good support from EMA coordinators.

The perceived administrative burden from the application process is to a degree linked to the chance of a positive outcome: those who prepare an application that is denied will experience a higher burden than those whose application is granted, even when the costs are the same. It is therefore of interest to know what percentage of all applications is unsuccessful. Data provided by the EMA lists only 23 applications as unsuccessful in obtaining a designation. Some have used this to suggest that the COMP is insufficiently critical in its initial assessment. What needs to be understood here, though, is that **the COMP offers applicants the opportunity to withdraw their application from consideration without public notice, when it is expected that the COMP will reject the application.** This may be the case if the potential sponsor is not able to demonstrate significant benefit based on the data available at the time. According to EMA staff, many such withdrawn applications are refiled once additional data has been collected.

The EMA does not keep records on how many applications are withdrawn prior to consideration or how many initially withdrawn applications are resubmitted later on. Therefore, **it cannot be established if the EU Orphan Regulation is inherently inefficient by inviting and reviewing large numbers of applications of insufficient quality.** Some COMP members have suggested, though, that the evidentiary standard for applications could be raised, as frequently submissions are received that are deemed to be of poor quality. However, it was acknowledged that this raises the threshold for first-time applicants with possibly limited understanding of the process.

Annual sponsor reports

The EU Orphan Regulation requires all sponsors to submit annual reports “on the state of development of the designated medicinal product”.²¹⁶ These reports include information on ongoing studies, the planned investigation activities and any anticipated or current problems in the development process.²¹⁷ In a discussion with COMP members it was noted that **the data included within these reports are not used for a specific purpose** and that the COMP has no formal task evaluating these reports. Information contained within the reports has been used on some occasions for academic research to better understand why and when product development fails (Pauwels et al., 2017), or what the orphan product pipeline contains (Morel et al., 2016).

Given this apparent lack of systematic use of the reports, it is **fair to ask if the requirement to submit these does not impose an unnecessary burden**

²¹⁶ Article 5(9) of the EU Orphan Regulation (EC) 141/2000.

²¹⁷ <https://www.ema.europa.eu/en/human-regulatory/research-development/orphan-designation/submitting-annual-reports-medicine-development>

on sponsors and should be abolished. However, as the reports contain potentially useful information that could further the field of orphan medicine development overall (e.g. by enabling the creation of a registry of products for which development was abandoned but that may still hold potential), perhaps the question should rather be **how better use of this information can be made.**

Marketing authorisation and maintenance of orphan designation

As with the initial application process, sponsors who have brought orphan medicines to market appear largely satisfied with the quantity and type of information required to confirm the orphan designation at the time of marketing authorisation (93% of 27 respondents report this as acceptable or better). Some note, however, that **the evidentiary proof required is more appropriate at the time of initial application than at marketing authorisation** when significant benefit needs to be demonstrated. Difficulties flagged relate primarily to uncertainty about what products need to be compared against, as some may have been authorised only shortly before (and clinical information was not yet publicly available) or because there are many different types of treatments to compare against. Also, comparison against products that have been granted conditional approval is considered challenging as for these products the data set may be immature.

Sponsors also express some dissatisfaction with what, in their view, is **unpredictability in the interpretation of the Regulation.** In particular, the 2016 Commission Notice specifying that extensions and variations to the marketing authorisation for authorised orphan medicines are now subject to reassessment by the COMP is seen as having upset the playing field (European Commission, 2016). It is indicated that this could lead to additional costs for sponsors who now may need to maintain two separate marketing authorisations.

Overall coherence and timeliness of procedures

The processes for application and assessment of all applications follow a strict timeline. According to representatives of the EMA and COMP, these timelines are adhered to, although 'delays' may occur when sponsors are requested to provide additional information. Over 65% of respondents consider the administrative requirements and timeliness of responses 'good' or 'very good'.

Reflections on administrative burden of the EU Orphan Regulation

The here presented analysis of the administrative burden associated with the EU Orphan Regulation is based on relatively limited quantitative information. Qualitative information provided by various groups of stakeholders, however, for the most part did not flag up major concerns among stakeholders that the administrative burden was disproportionate. However, one particular area that merits attention is **the increasing administrative burden imposed on the home institutions of COMP members.**

It was noted that in the years since the Regulation came into effect, the number of applications has increased dramatically. Whereas in the early days of the Regulation, the COMP's monthly meetings lasted a single day, they currently take three full working days. COMP representatives have indicated that trends

in their workload mean an additional day (a 4-day meeting) may even become necessary in the future. This poses a significant challenge to the home institutions of COMP members, who typically hold positions in governmental, clinical or academic institutions. Since these institutions are not reimbursed, this can make it hard for COMP members to take the time required to attend the full meetings. However, voting on designation requires that quorum is reached so attendance of a sufficient number of members is essential. Unlike some other EMA committees, the COMP also does not allow for the use of 'alternates'. The majority (n=21, 70%) of surveyed representatives of national public authorities considered the fact that **the orphan designation process is exempt from the EMA fee system, and that COMP members are not reimbursed, a potential threat to the long-term sustainability of the system**. Whilst some interviewees suggested that sponsors could be asked for a more substantial contribution into the system, it was emphasised that the fee waivers and reductions for initial applications should not be changed as this is an important incentive for smaller sponsors.

In interviews, COMP members offered several suggestions on ways to potentially improve the efficiency of COMP proceedings and thereby reduce the burden. This includes limiting the number of oral explanations, by inviting sponsors only when there is sufficient disagreement or doubt among COMP members regarding the decision-making. As mentioned previously, another suggestion involved raising the evidentiary standard for applications. On the desirability of the use of alternates opinions in the COMP were substantially divided.

8.6. Concluding remarks on the efficiency of the EU Orphan Regulation

The reasonableness of the costs and benefits

Our analysis showed that, in the context of the EU Orphan Regulation, various types of costs and benefits could be identified, while at the same time the cost for one stakeholder reflect the benefits for another stakeholder. This resulted in broad set of costs and benefits for various stakeholders, which altogether determines the level of efficiency.

The analysis also showed that, from the perspective of availability of and access to orphan medicines, there are three types of impact as a result of the EU Orphan Regulation. The analysis has some limitations, as assumptions had to be made. Nevertheless, based on the analysis the following impacts were determined: (1) there is an impact on the availability of orphan medicines in the EU: **18 to 24 additional orphan medicines have been developed** as a direct result of the Regulation; **(2) orphan medicines became available in the EEA 9 months faster; and (3) three years after market introduction orphan medicines are available in more Member States. This impact translates to extra availability for 2.7% of EU population. It is also found that orphan medicines in the longer run find their way to more EU Member States.**

The additional development of orphan medicines means that developers have increased their R&D expenses; these (global) expenses are on average €602 million per orphan medicine and have been incurred in the 10 years preceding

market introduction. The industry has also earned extra sales revenues due to the additional availability and extra accessibility of orphan medicines in the EU. These extra sales revenues in combination with the extra protection (market exclusivity) from competition can be regarded as compensation for the R&D costs. Based on an analysis for four orphan medicinal products that experienced generic competition in 2015-2017, this compensation is assessed to be on average 30% in the years of extra protection offered by the market exclusivity (which is on average 3.4 years). The cost benefit analysis shows no firm conclusion as to whether the extra revenues resulting from the EU Orphan Regulation exceed the additional R&D investments.

For the **health system** the extra costs consist of the extra use of orphan medicines resulting from the EU Orphan Regulation, the additional health costs associated with treatment with the orphan medicine and savings of health costs of alternative treatment. A net effect could not be established at the level of the EU Orphan Regulation, as this information is lacking for many orphan medicines. Also, the wider economic benefits could not be established at the level of the EU Orphan Regulation, mainly due to the large variation in diseases targeted by the orphan medicines. It is likely to be a positive value, though, given the fact that rare diseases are often highly disabling and represent a heavy burden for all.

The exact distribution of health care expenses between public parties and **patients** is not clear. However, we have assumed that in the EU the vast majority of health care costs are borne by public parties, either through health systems or through health insurance.

Health benefits have been assessed by using information on the Incremental Cost-Effectiveness Ratio (ICER), which were found in HTA reports for 24 active orphan medicines.²¹⁸ The average ICER for these products is €110,000. Using the realised sales of these orphan medicines in the EU, also a weighted average ICER has been calculated, at €54,000 per QALY.²¹⁹ For several reasons the weighted average could be an underestimation for the EU28, reason why it is used as the lower limit of the range that has been applied (with unweighted average as upper limit). Using this range, **the EU Orphan Regulation is estimated to have resulted in a gain of 210,000 to 440,000 Quality Adjusted Life Years.**

Whilst these estimates of costs and benefits to different groups of stakeholders are informative, they cannot directly answer the question of whether this balance of costs and benefits is proportional or 'fair'. This is in essence a subjective assessment based on the value placed on health gains and on what is considered a reasonable profit margin. The here calculated average 'cost per QALY' of €54,000 per QALY is above what is used by some payers to determine

²¹⁸ These 24 orphan medicines represent 52% of recorded overall orphan sales in 2016 in the EU.

²¹⁹ In calculating the weighted average ICER, the ICERs of the orphan medicines are weighted by their EU sales revenues: orphan medicines with higher sales revenues in the EU have a higher weight than those with lower sales revenues. The fact that the weighted ICER for these 24 orphan medicines is much lower than the unweighted ICER reflects the higher sales revenues for orphan medicines with a lower ICER.

a general threshold value for reimbursement.²²⁰ Nonetheless, even medicines that are assessed to exceed such threshold values are sometimes reimbursed if a convincing argument was made for why this should be the case. The decision-making can be shaped also by advocacy and public opinion. This indicates that within societies there is a substantial willingness to pay for medicines to treat rare diseases, sometimes at a (very) high cost. At the same time, public debate is increasingly focussed on the prices of medicines. Although this discussion is not limited to orphan medicines, this set of products has received particularly scrutiny because of the incentives (market exclusivity) offered. The important question then is whether the prices charged for medicines for which the development was partially supported with public funding and to which additional monopoly rights are granted are reasonable in relation to the investments of the developer. The here presented analyses suggest that, for most orphan medicines, the level of compensation offered by the market exclusivity is reasonably balanced with the R&D costs. At the same time, cases can exist where there is significant 'overcompensation'. It is ultimately a societal judgement whether the regulatory system should provide space for such cases and accept them as an inherent part of a system that has winners and losers in the form of more and less commercially successful products, or whether it should in some way 'cap' the rewards those winners can reap.

Possibility for cost savings

Improvement of the efficiency of the Regulation (the cost-benefit ratio) can be achieved by reducing costs (and keeping impacts) or by improving impacts (at same costs). We first concentrate on the cost items as shown in the cost-benefit analysis.

One cost element is formed by the administrative costs of the Regulation. Although these costs are relatively minor, they could be reduced in various ways. EMA and national representatives in the COMP spend a substantial amount of time on the evaluation of applications for orphan designations that do not translate into additional authorised orphan medicines. A relatively small cost saving (less than €1 million per annum) can be realised if this process could be optimised, for instance by raising the evidentiary requirements at application.

A much larger costs element relates to the health costs resulting from the treatment of patients with orphan medicines. These costs depend on the price level of the orphan medicines. In this respect the market exclusivity reward provides the opportunity for sponsors to have a longer period in which the product is protected from competition and higher prices can be realised. In this respect efficiency gains can be realised if the market reward would be related to the R&D costs.

²²⁰ For instance, the National Health Care Institute in the Netherlands has established a reference value of €50,000 per QALY for conditions with an average disease burden and of €80,000 per QALY for conditions with a high disease burden. (<https://www.zorginstituutnederland.nl/publicaties/rapport/2015/06/26/kosteneffectiviteit-in-de-praktijk>) In the UK, the National Institute for Health and Care Excellence (NICE) considers an intervention cost-effective if it has an ICER below GBP 30,000 (approx. €33,400) per QALY. (<https://www.nice.org.uk/media/default/about/what-we-do/our-programmes/developing-nice-guidelines-the-manual.pdf>)

With respect to relation between R&D costs, product prices and market rewards various situations are described that may involve unintended use or effects of the system:

- Indication stacking: products that have been authorised for multiple orphan indications have a larger patient basis and can thus realise more turnover than a typical orphan medicine. Moreover, consecutive periods of market exclusivity prolong the protection period, thereby increasing the risk of overcompensation. By applying different rules for market reward in case of multiple indications for the same product, the risk of overcompensation and thus high costs for the use of orphan medicines can be reduced
- Repurposed medicines, including well-established use products and known active substances: The current regulatory framework for the EU Orphan Regulation does not contain any provisions to safeguard the affordability and accessibility of orphan medicines even when no significant R&D investments have been made by the sponsor. Sponsors of orphan designated products authorised as well-established use products and known active substances receive the same reward as developers of new active substances.

In both cases the market reward may result in overcompensation, taking into account the R&D costs, the economic value of the market protection and the length of the market exclusivity reward. As shown in Section 5.8, in case of an "average" orphan medicine there is a risk over overcompensation if turnover levels are high (in our analysis 14% of orphan medicines showed an annual turnover of €100m or more). In case of multiple authorised orphan indications this level may be reached more easily. In case of repurposed products (including well-established use products and known active substances), overcompensation may occur because the R&D costs may be "below average".

We do not have good data on the number of instances where there has been such an imbalance between the costs of development of the orphan medicine in question and the rewards reaped by sponsors. However, in case the additional market protection can be related to the actual development costs and/or sales revenues in the EU, the risk of overcompensation and consequently the costs to society would reduce.

A third possible area that would help to improve the cost-benefit ratio of the EU Orphan Regulation relates to the outcome of the Regulation, i.e. the health impact. Our analysis indicates that the orphan medicines with relatively low ICERs are used more than those with high ICERs (see Section 8.2.5). We also notice that for many orphan medicines such an analysis is not available. This means that decisions to allow orphan medicines to enter national markets may not always be based on cost-effectiveness observations. If more extensive economic information would be available, it could assist in better-informed decision making by authorities.

Administrative burden

Developers of (potential) orphan medicines are not required to apply for orphan designation or to make use of the incentives offered under the EU Orphan Regulation. The Regulation does not impose any requirements upon developers

that choose not to make use of this possibility. As such, there is no significant administrative burden on this group of stakeholders. Although sponsors of orphan designated medicines must abide by the requirements laid down in the EU Orphan Regulation framework (e.g. to submit annual sponsor reports), they also have the ability to withdraw their orphan designation at any time. Although the administrative burden could not be quantified, sponsors generally did not report perceiving the EU Orphan Regulation as imposing an unreasonable burden and appear generally satisfied with the regulatory framework and its application.

There is some administrative burden resulting from the Regulation at the level of the EMA. This burden is relatively small but is likely set to increase as the number of applications continues to grow. The issue of increasing workload likewise affects the members of the COMP. The administrative burden associated with the work performed by COMP members largely falls on the institutions from which these members are drawn, and which are not compensated for this. Our analysis found that this is putting serious strain on the system and could affect its long-term sustainability.

9. Coherence

The EU Better Regulation guidelines for evaluation offer the following guidance for assessing the coherence of EU actions:

Coherence

The evaluation of coherence involves looking at how well or not different actions work together. It may highlight areas where there are synergies which improve overall performance or which were perhaps not possible if introduced at national level; or it may point to tensions e.g. objectives, which are potentially contradictory, or approaches which are causing inefficiencies.

Source: Better Regulation Toolbox, #Tool 47.

In evaluating the coherence of the EU Orphan Regulation, the study has drawn on desk research and stakeholder consultations to consider the extent to which it is coherent with other EU actions, both legislative and non-legislative, with which it shares certain objectives. Additionally, the study has explored how the Regulation works alongside other actions at the national level. The question essentially is thus whether the Regulation fits within a holistic architecture or if it in places confuses or obstructs other efforts.

The study has focused on the following evaluation questions:

- To what extent is the Orphan Regulation coherent/complementary with other EU and national interventions in the pharmaceutical area (e.g. legal interventions for medicinal products in general, paediatrics medicines, research programmes, national pricing mechanisms)?
- To what extent are the various tools (incentives, procedures, assistance) as set out in the Orphan Regulation working together in a coherent way?
- What are the links between the areas of orphan and paediatric medicines? To what extent, in practice, is there an overlap and how has these influenced therapeutic advances?
- To which extent is the concept of designation consistent with the marketing authorisation itself?

We address the questions through consideration of the data obtained through our principal data collection methods, including targeted interviews with key stakeholders, consultations with industry and national authorities and extensive desk research, and a discussion with members of the COMP.

The qualitative research provides insight to complement the more objective but limited analysis of legal texts for example. The wider literature has also helped to validate the feedback from stakeholders, many of whom do not have a view of all relevant legislation and associated wider policy initiatives.

9.1. Coherence with other EU Regulations

The EU Orphan Regulation exists alongside various other EU Regulations with which it shares certain objectives, or the effects of which affect its application. The main Regulations to consider here are:

- Regulation No 469/2009 concerning the **supplementary protection certificate** for medicinal products (The European Parliament and Council, 2009) (replacing Regulation 1768/92);
- Regulations No 1901/2006 and 1902/2006 on medicinal products for **paediatric use** (The European Parliament and Council, 2006);
- Regulation No 1394/2007 on **advanced therapy medicinal products** (The European Parliament and Council, 2007);

Recently, the European Commission published a series of studies that assessed various aspects involving the first two of the Regulations listed. The first was a study on the economic impact of the Paediatric Regulation, including its rewards and incentives (Varnai et al., 2016). A second study, by Copenhagen Economics, more broadly analysed the economic impact of SPCs and pharmaceutical incentives and rewards in Europe (Copenhagen Economics, 2018).

Third, researchers from the Max Planck Institute examined the functioning of the Supplementary Protection Certificate (SPC) system from a legal perspective. (Desaunnetes et al., 2018) and a 2018 study for the Ministry of Health in the Netherlands likewise explored interactions between the SPC system, the paediatric extension, the orphan market exclusivity and other regulatory incentives (de Jongh, Radauer, Bostyn, & Poort, 2018).

Our analysis did not explore the above Regulations in detail. Rather, it focused on their points of interaction with the EU Orphan Regulation.

Each of these studies notes that the different Regulations intersect with each other in various ways. Developers of orphan medicines can benefit from incentives and rewards offered by each of the Regulations, depending on product characteristics. As demonstrated by the data presented in Section 5.6, SPC protection can be, and frequently is, concurrent with orphan market exclusivity. By contrast, the paediatric SPC extension is incompatible with the orphan market exclusivity, which means that developers eligible for either of the rewards are forced to make strategic decisions.²²¹ The following Sections explore some of these interactions and their consequences in more detail.

The majority of respondents to the survey of national public authorities (22 respondents or 61%) agree or strongly agree with the statement that the EU Orphan Regulation is “coherent with other EU policies and actions that support

²²¹ Recital 29 of the paediatric Regulation (1901/2006/EC) notes that products designated as orphan medicinal products under the rules of the Orphan Regulation (No 141/2000/EC) will be granted 10 years of market exclusivity on the granting of a marketing authorisation for the orphan indication. The recital goes on to note that orphan medicines are often not patent-protected, and that the paediatric reward of a supplementary protection certificate (SPC) extension cannot be applied if they are patent-protected, such an extension would provide a double incentive. Therefore, for orphan medicinal products, instead of a 6-month extension of the SPC, the 10-year period of orphan market exclusivity should be extended to twelve years, where the requirement for data on use in the paediatric population is fully met.

development of pharmaceutical products". Academic researchers and experts largely agree with this statement as well.

9.1.1. Supplementary Protection Certificate

The Supplementary Protection Certificate (SPC) was first introduced in the EU in 1992.²²² Its purpose is to compensate developers of medicinal products for the effective loss of term of protection from their patents resulting from the fact that, before a product can be marketed, preclinical and clinical research needs to be conducted to demonstrate effectiveness and safety. In principal, all authorised medicinal products can benefit from a period of protection from an SPC. The SPC duration is dependent on the time between the date of filing of the corresponding patent and the date of issuance of the first marketing authorisation in the EEA and cannot exceed five years. To be eligible for an SPC a product must:²²³

- Be protected by a basic patent that is in force;
- Have been granted a marketing authorisation somewhere in the EU;
- Not have been protected by an SPC before and
- The marketing authorisation must be the first authorisation in the EU to place the product on the market as a medicinal product.

The SPC protection exists separately from the market exclusivity for designated orphan medicines. One important difference between the two types of protection lies in the ability to accumulate protections. An orphan medicine can benefit from multiple periods of market exclusivity, if it has more than one orphan designation since each designation, upon authorisation for the corresponding orphan indication, confers a separate 10-year period of market exclusivity. By contrast, as the above criteria show, a product can in principle only benefit from one SPC. However, in recent years, the notion of 'one product, one SPC' has been challenged such that it is now possible for a product to have more than one SPC if there are multiple applicable patents. A full discussion of this is outside the scope of this study (de Jongh et al., 2018; Desaunnetes et al., 2018).

A further difference between the two forms of protection is that SPCs, whilst governed by an EU Regulation, are granted at a national level,²²⁴ whereas the orphan designation and the corresponding market exclusivity are granted at the EU level. This means that it is possible that a product is under SPC protection in one country, but not or no longer in another country. Therefore, it is possible

²²² See Council Regulation (EEC) No 1768/92 of 18 June 1992 concerning the creation of a supplementary protection certificate for medicinal products, which entered into force on 2 January 1993. This original law has been replaced by Regulation No 469/2009, which came into force in May 2009.

²²³ Article 3 of the Regulation concerning the supplementary protection certificate for medicinal products (No 469/2009/EC).

²²⁴ Article 9 (1) of Regulation 469/2009/EC states that the application for an SPC shall be lodged with the intellectual property office of the Member State that granted the basic patent.

that overall protection levels on an orphan medicine differ from one country to another.

Representatives of orphan medicine developers and their trade associations interviewed for this study agreed that the full constellation of protections offered by the SPC and orphan Regulations (as well as other Regulations that confer IP or regulatory protections) benefits pharmaceutical innovation in general and of orphan medicines in particular. None of the developers or trade associations remarked on any tensions between the SPC Regulation and the orphan market exclusivity (nor any other aspects of the EU Orphan Regulation). By contrast, a contributor representing a national competent authority argued that the regulatory framework as a whole (not specifically referring to the SPC Regulation) lacks coherence and gives developers too much ability to strategically 'hop' between systems. The representative believes this leads to market unpredictability for generic manufacturers and health payers. Other interviewees did not comment specifically on the interaction between the SPC Regulation and EU Orphan Regulation.

9.1.2. Paediatric Regulation

Pharmaceutical innovation is driven to a large extent by the promise of financial reward. Similar to the market for treatments for rare diseases, the market for individual paediatric medicines is comparatively small and consequently research is often not focused on paediatric populations. Moreover, practical and ethical concerns about research in children have meant that, even for products for which there is both an adult and paediatric market, frequently no studies are undertaken for paediatric use that would be necessary to establish if the product is suitable for children or to develop a suitable formulation or dosage guidelines. To improve this situation, in 2006, the Paediatric Regulation was introduced.²²⁵

Recital 4 of the Paediatric Regulation defines the aim of the Regulation, which is "to facilitate the development and accessibility of medicinal products for use in the paediatric population, to ensure that medicinal products used to treat the paediatric population are subject to ethical research of high quality and are appropriately authorised for use in the paediatric population, and to improve the information available on the use of medicinal products in the various paediatric populations. These objectives should be achieved without subjecting the paediatric population to unnecessary clinical trials and without delaying the authorisation of medicinal products for other age populations." (1901/2006/EC).

The Paediatric Regulation mandates the development of a so-called '**Paediatric Investigation Plan**' (PIP) for studies and research in paediatric populations.²²⁶ The requirement applies to all new marketing authorisation applications filed,

²²⁵ 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 1902/2006.

²²⁶ The requirements for the PIP are set out in Chapter 3 of the paediatric Regulation (1901/2006/EC).

unless the applicant is granted a waiver from this obligation. The requirement to submit a PIP is waived for specific medicines or classes of medicines that²²⁷:

- are likely to be ineffective or unsafe in part or all of the paediatric population;
- are intended for conditions that occur only in adult populations; and
- do not represent a significant therapeutic benefit over existing treatments for paediatric patients.

For those medicinal products that are already authorised, and which are still under patent protection or SPC protection, a PIP is mandatory²²⁸ in case of extensions or variations on the existing marketing authorisation. In those cases, the PIP should cover both the existing and the new indications, pharmaceutical forms and routes of administration (de Jongh et al., 2018).

For medicinal products that are still under patent protection, the system provides for a one-off **six-month extension of SPC protection** upon compliance with an approved PIP.²²⁹ It is not required to obtain a marketing authorisation for a paediatric use, nor is it necessary to file for one. This paediatric extension to the SPC, however, is not compatible with the orphan market exclusivity in that the same product cannot benefit from both types of protection. The reason given for this is that "As [orphan medicines] are frequently not patent-protected, the reward of supplementary protection certificate extension cannot be applied; when they are patent-protected, such an extension would provide a double incentive."²³⁰ Rather, designated orphan medicines for which an approved PIP has been completed, can receive an additional two years of market exclusivity. A sponsor can, however, choose to withdraw the orphan designation to become eligible again for the paediatric SPC extension.

This ability to 'switch' between protection systems can create uncertainty for developers of generic or biosimilar products that wish to reference the product as it is not clear when the protections on the product will expire. For instance, Novartis had obtained an orphan designation for *Glivec* (imatinib mesilate) for treatment of chronic myeloid leukaemia (CML). It benefited from the full 10 years of orphan market exclusivity for this indication. It also had completed an approved PIP and was thus eligible for a further 2-year extension.²³¹ Meanwhile, the company had obtained several additional orphan designations and had obtained authorisation for a separate orphan medicine, *Tasigna* (nilotinib), for the same orphan indication. It was

²²⁷ <https://www.ema.europa.eu/en/human-regulatory/research-development/paediatric-medicines/paediatric-investigation-plans/class-waivers>

²²⁸ Paragraph 11 of the Paediatric Regulation (1901/2006/EC).

²²⁹ Paragraph 26 and Article 36(1) of the Paediatric Regulation (1901/2006/EC).

²³⁰ Paragraph 29 of the Paediatric Regulation (1901/2006/EC).

²³¹ See, for instance: "The Hague Court confirms paediatric extension of SPC for former EU orphan drug imatinib". (2016) Lexology. <https://www.lexology.com/library/detail.aspx?g=c45e5f48-de26-46f6-afc8-8c13c2eabb63>

possible for Novartis to obtain consecutive marketing authorisations for both Tasigna and Glivec, even though the products were similar, as it had granted itself consent, using the provisions laid down in Article 8(3)(a) of the Regulation. Subsequently, Novartis opted to withdraw the other orphan designations on Glivec, which allowed the company to receive the 6-month paediatric SPC extension whilst it still benefited from the market exclusivity on *Tasigna*, for which the therapeutic indications overlap with that of *Glivec*. A generic manufacturer, Teva, tried to block Novartis from benefiting from both systems, claiming that Novartis was not entitled to a paediatric SPC as *Glivec* had once been approved as an orphan medicine. This reading was, however, rejected by the Court (District Court the Hague, 2016). The decision was then appealed by Teva, but was upheld by the Court of Justice of the EU (CJEU, 2016).

Of note is that the rationale provided in the Paediatric Regulation for offering a 2-year extension of the market exclusivity for orphan medicines rather than an SPC extension (namely that orphan medicines are “frequently not patent-protected”) is at odds with the data presented in Section 5.6: these showed that 70% of orphan medicines was still under patent or SPC protection at the time of marketing authorisation and for 69% of these (so 48% of orphan medicines) that protection was still in effect by the end of the 10-year market exclusivity. For these products, the Paediatric Regulation states that the 6-month paediatric extension of the SPC would provide a “double incentive”. Whilst this is technically correct, it is noteworthy that this apparent intent to avoid double incentives evidently does not apply to the combination of the ‘normal’ SPC protection and the orphan market exclusivity. Moreover, it is plausible that this double protection is in practice often less attractive to developers (particularly when they largely overlap) than the 2-year extension of the market exclusivity. The current incentive therefore may be more valuable than the double incentive the Paediatric Regulation sought to avoid. These findings **call into question whether the underlying rationale for offering a 2-year extension of the market exclusivity for products for which the developer has completed an approved PIP is sound, and if this is the most suitable incentive.** Neither developers nor any other stakeholders, however, openly questioned the incentive or the underpinning rationale. Rather, stakeholders focussed on the interplay and effectiveness of the EU Orphan Regulation and Paediatric Regulations.

The main concern raised by stakeholders – primarily those outside of industry – is the limited development of products suitable for children with rare diseases that was shown in Section 5.4.5 and discussed also in Section 7.4. The disproportionate focus on conditions that affect (also) adults compared to primarily paediatric conditions, indicates that even the two Regulations together are not sufficiently able to incentivise development of paediatric medicines. Importantly, **neither the EU Orphan Regulation nor the Paediatric Regulation offers incentives for successful development of medicines for use in children.** The incentives, albeit the 6-month SPC extension or the 2-year market exclusivity extension, are provided in reward for compliance with

an agreed PIP, regardless of the outcomes of those paediatric investigations.²³² This decision is understandable from the perspective that all information on safety and efficacy for paediatric use is valuable. However, the consequence could be that developers aim to minimise the requirements imposed by the PIPs or seek PIP waivers rather than actively develop products suitable for children. Whilst some stakeholders from outside industry voiced concerns that this could be the case, there is no data to support this suggestion.

As discussed also Section 7.4, the lack of paediatric development of orphan medicines has been particularly noticeable for **paediatric cancers**. Here, some stakeholders from patient organisations and academia, have pointed out there is a measure of **tension between the Paediatric Regulation and the Orphan Regulation**. Article 11 1(b) of the Paediatric Regulation, which defines the conditions for a PIP waiver, states that a waiver is granted if a condition does not exist in children.²³³ The rationale behind this is to avoid unnecessary and unethical trials in children. However, it allows for a waiver to be granted even when the product could exhibit cross-reactivity to a target for a condition affecting children. The European Society for Paediatric Oncology (SIOPE)²³⁴ advocates **a new approach to the consideration of waivers from paediatric investigations: rather than look narrowly to see if the condition occurs in children, assessors should also consider the mechanism of action of the product**. By way of example, the SIOPE representative suggested that whilst lung cancer does not exist in children, a medicine developed to treat lung cancer may also be effective in children because the mechanism of action of that medicine can target other forms of cancer as well. It is recognised this would not do much for existing medicines that are now used off-label in children, because there is no requirement anymore for paediatric development but could be of use for new products.

It is important to note that the EMA is required to amend the lists of waivers as knowledge of science and medicine evolves over time,²³⁵ with the current list of class waivers having been published in July 2015.²³⁶ The review revoked the waivers for all medicines to treat kidney and renal pelvis carcinoma on the grounds that the condition does occur in the paediatric population(s), and

²³² Paragraph 28 of the Paediatric Regulation (EC) No 1901/2006 states: "Because the reward is for conducting studies in the paediatric population and not for demonstrating that a product is safe and effective in the paediatric population, the reward should be granted even when a paediatric indication is not authorised."

²³³ Article 11 of the Orphan Regulation (141/2000/EC) comprises a list of three types of waivers where there is evidence showing a medicinal product is (i) likely to be ineffective in paediatric populations, (ii) intended for conditions that occur only in adult populations, (iii) and does not represent a significant therapeutic benefit over existing treatments.

²³⁴ <https://www.siope.eu/>

²³⁵ See Recital (13) of the Orphan Regulation (141/2000/EC)

²³⁶ The Paediatric Committee (PDCO) adopted a review of the class waiver list in July 2015, which contains the updated list of classes of medicines and includes a scientific discussion as regards the rationale for the revision of the class waivers. It supersedes all previous class waiver decisions. <https://www.ema.europa.eu/en/human-regulatory/research-development/paediatric-medicines/paediatric-investigation-plans/class-waivers>

clinical studies may fulfil a therapeutic need of the paediatric population. Equally, there were revised waivers for various cancers on the grounds of poor efficacy or limited additional therapeutic benefit in affected paediatric populations. The **revised class waiver list** came into effect in July 2018 mid-way through this study, and as such the impacts of this change on the granting of PIP waivers for products that could be of benefit to paediatric populations is not yet understood.

Another possible reason for the shortage of new treatments for paediatric cancers may stem from the fact that **certain cancers that affect both adults and children are not sufficiently 'rare' to be eligible for orphan designation**. The question then is if the paediatric form, by itself, can be considered a valid sub-set for defining an orphan condition. Under the EU Orphan Regulation, the aim normally is to use the widest possible scope for any condition, thus including both adult and paediatric populations.²³⁷ However, sometimes this would mean that the total population exceeds the prevalence threshold for orphan designation. Developers of for such products thus cannot benefit from the incentives offered by the EU Orphan Regulation, whereas the Paediatric Regulation encourages trials in paediatric populations but does not specifically reward successful development for paediatric use. Development of treatments for affected children thus effectively falls between the cracks of the two Regulations. A COMP representative indicated that, in such cases, the CHMP sets the final indication. **By defining separate indications for paediatric and orphan populations, the EU Orphan Regulation can provide incentives to stimulate product development for paediatric populations.**²³⁸ One interviewee indicated that there has been an internal working group between the CHMP and COMP to discuss orphan conditions and whether these should encompass the entire population, meaning both adults and children, for the designation.

A representative from a patient organisation questioned whether there is sufficient awareness of the interplay between the two Regulations across industry and specifically the fact that the EU Paediatric Regulation offers two years additional market exclusivity for paediatric development of an orphan medicine. This was offered as a possible reason why sponsors of orphan medicines are lagging in the development for paediatric indications. However, this statement was not corroborated by independent data from sponsors, most of whom in our discussions appeared to be well aware of the two Regulations and their interplay.

Most representatives of national public authorities agreed or strongly agreed with the statement that the EU Orphan Regulation is "coherent with other EU policies and actions that support development of pharmaceutical products."

²³⁷ Section D (1) of the Commission notice on the application of the Regulation, notes that: 'When evaluating an application for designation, the COMP should consider an orphan condition in broad terms in order to avoid designations relating to artificial subsets of a particular condition. Commission notice on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products (2016/C 424/03)

²³⁸ Only doing so when considering the adult and paediatric populations together would render the entire indication not eligible for orphan designation.

Nonetheless, consistent with the above observations from stakeholder interviews, areas of tension were seen primarily in the interaction with the Paediatric Regulation and in the scope of definition for a condition.

9.1.3. ATMP Regulation

The most recently introduced Regulation to have some overlap with the EU Orphan Regulation is the Regulation on Advanced Therapy Medicinal Products (ATMPs).²³⁹ This Regulation lays down when a product can be classified as an ATMP, distinguishing between different types of ATMP. It offers developers of designated ATMPs a set of scientific and financial incentives to encourage development of advanced therapies, which include amongst other things reductions in the fees payable to the EMA for scientific advice or its certification procedure.

As discussed in Section 4.1.2.4, these incentives relate primarily to services offered by the EMA. No additional protections can be derived from ATMP classification and the classification is optional. Although the number of ATMPs under development has been steadily increasing (see Section 6.3.1), stakeholders interviewed for this study had few insights into the interaction between the ATMP and the EU Orphan Regulations. That said, one sponsor actively working on development of ATMPs for treatments of rare diseases affecting children emphasised the **importance of developing and reviewing all Regulations as part of a holistic regulatory system**. This call was echoed by some other stakeholders as well.

In the discussion of the implications of ATMPs for the application of the regulatory framework for orphan medicines presented in Section 6.3.1, the specific challenge associated with demonstration of significant benefit for ATMPs, where there is often limited clinical evidence, was addressed. This challenge is, however, associated more with product characteristics of ATMPs than with any apparent lack of coherence between the ATMP Regulation and the Orphan Regulation.

Section 4.5.2 explained how, with the advent of ATMPs, new ways of defining and assessing similarity were introduced wherein ATMPs are evaluated on the basis of biological and functional characteristics. Discussions with EMA and COMP members have made it clear that, even with this guidance, **in practice the assessment of similarity** (which is done by the CHMP rather than by the COMP) **for ATMPs can be challenging** as it can involve also considerations of manufacturing technologies used or certain safety attributes.²⁴⁰ The relatively small (albeit growing) number of such applications reviewed to date also means that there is limited experience within the COMP.

²³⁹ Regulation No 1394/2007/EC on Advanced Therapy Medicinal Products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004.

²⁴⁰ Questions and answers related to the assessment of similarity for advanced therapy medicinal products ("ATMPs") in the context of the orphan legislation. (2018). EC https://ec.europa.eu/health/sites/health/files/files/orphanmp/doc/2018_qa_atmps_en.pdf

9.2. Internal coherence

9.2.1. Coherence between incentives

As set out in various other Sections of this report (3.3 outlining the design of the Regulation, Section 7.1 on the effectiveness of different incentives), the Regulation contains various tools that should work together to support the development of new orphan medicines.

Interviewed sponsors indicated that each of these tools or incentives serve a particular purpose that address different aspects and pressure points across the innovation lifecycle. **The fee waivers, protocol assistance, market exclusivity and (encouragement) of support for research all come together to create a stronger policy response to unmet medical needs than would any one of those incentives in isolation.** They are synergistic and not disconnected or confused.

Sponsors also noted that the relative value of each incentive may differ across businesses and products, depending on the experience of the developer or certain characteristics of the product under development.

Our desk research confirms the tools work together in a coherent way, in as far as protocol assistance helps developers to better understand what is required to meet the criteria for obtaining orphan designation and for maintaining this designation to obtain the market exclusivity reward.

Access to additional research incentives (referred to as 'aid for research'), and fee waivers are of additional value to developers, particularly to smaller and less experienced developers with fewer resources at their disposal.

Our survey results also suggest there is a good degree of internal coherence. We found no indications of any particular lack of coherence between any of the tools that make up the EU Orphan Regulation. Rather, most respondents (27, 73%) agreed or strongly agreed that the various tools offered within the context of the EU Orphan Regulation work together in a coherent way.

9.2.2. Coherence between designation and marketing authorisation

A further aspect of internal coherence concerns **the relationship between orphan designations and products that ultimately are authorised with maintenance of the orphan status.**

Data presented in Section 5.2 show that only a small proportion of designations (~7-8%) have reached the market. That is not to say that there is not potential for additional authorised orphan medicines, even if no further designations were granted, but the **conversion rate is approximately 10-12%**. One could ask if this relatively low share of products that go on to become orphan medicines implies that there is a lack of coherence between the concepts of designation and marketing authorisation.

In discussion with COMP members, this interpretation was contested. It was noted that this **low conversion rate can be attributed to the general complexity and risk associated with any drug development process** and is broadly comparable with the 10-12% success rate estimated for new

medicines more generally.²⁴¹ Therefore, it is felt **this does not reflect any issues with the design and internal coherence of the EU Orphan Regulation.**

A related area where there is arguably **some degree of internal incoherence is between the orphan indication** that is associated with the designation, **and the actual therapeutic indication** of the authorised product. The orphan indication is decided upon designation, which can be early on in the process when the exact area of application of the product is not yet clear. It can be revised as the medicine is developed and results of clinical trials become available. The COMP purposefully sets relatively broad indications, considering the full prevalence of the condition rather than that of a sub-set. However, upon marketing authorisation, the CHMP may decide on a considerably narrower therapeutic indication, based on the clinical evidence. This means that in practice **there may be products on the market that are not eligible for orphan status as the prevalence of the condition it targets exceeds the threshold, even though the treatment population based on the therapeutic indication may fall well within this.** We have no data to determine how often this occurs, or whether this feature poses a barrier to pharmaceutical product development overall (keeping in mind that developers rarely can predict the precise therapeutic indication in early stages of development).

In determining whether a product with an orphan indication can be authorised when another product for that same orphan indication is still under market exclusivity, an assessment is made of the similarity between the products. **The similarity assessment considers, among other things, the therapeutic indications of the compared products.** What this means in practice is that there may be multiple products on the market for the same orphan indication, but that in reality serve the needs of different sets of patients. It is important to bear this mind in any discussion about clustering around indications.

Based on the above analysis, **one could argue that there is a lack of coherence between the concepts of designation and authorisation, but it is not evident that this is problematic.**

9.3. Coherence between different EMA assessment procedures

This Section explores the extent to which the different EMA assessment committees and procedures for assessment of orphan medicines interact. Depending on the type of product and orphan indication, a product may be assessed by up to four different EMA committees: the COMP for the orphan designation, the PDCO for approval of the PIP, the CAT for classification as ATMP and for preparing a draft opinion on the product's quality, safety and efficacy, and the CHMP for the benefit-risk assessment required for marketing

²⁴¹ See page 3 of the report, Clinical Development Success Rates 2006-2015, Bio, Biomedtracker and Amplion.

authorisation.²⁴² Additionally, a sponsor may receive protocol assistance from the Scientific Advice Working Party (SAWP).

As discussed in Section 4.2.2, all committees are made up of representatives of the EU Member States. Some members are also involved as experts in other committees or working parties.

Representatives of the EMA and COMP indicated **there is generally good collaboration between the different committees and working groups**. The overall opinion was that the committees work reasonably well together and that there are no major issues. COMP members identified two main areas where there had been occasional challenges:²⁴³

- The PDCO and COMP use different chronology for development with sponsors also submitting different data to each committee. This can make scientific discussions difficult as they lack common ground
- The timeline associated with decision making is different for both CHMP and COMP. This requires some consideration (possibility for COMP opinion after CHMP opinion to allow time for the scientific discussion at COMP once the final therapeutic indication has been defined), as the current timelines have caused issues in the past and are currently being challenged due to the scientific and regulatory aspects of some procedures, especially conditional marketing authorisations, accelerated assessment or the '8+2+1 procedures' for data exclusivity and market protection in which CHMP and COMP use very similar terminology in spite of different aims of the underlying frameworks

The issue raised by COMP members regarding the sometimes inconsistent use of terminology was echoed by some developers and representatives of national public authorities. They remarked that **concepts used by different Regulations, such as between 'unmet medical need' and 'major public health interest' or between 'significant benefit', 'clinically superior' (in the US) and 'added benefit' (in HTA) are seemingly similar but are used differently depending on context**.

OMP developers participating in the survey were asked to rate the coordination between the different EMA committees (i.e. COMP, PDCO, CHMP and CAT) involved in the assessment of EU designated orphan medicines. **The majority of respondents were broadly positive about the coherence of the various committees' activities**. The clarity of communication and the timeliness of assessments were most widely rated as being coherent.

The respondents were less positive about the consistency of outcomes and, in particular, the alignment and coherence of procedures among committees. Out of 35 respondents, 6 (17%) consider the alignment and coherence of procedures 'poor'. These respondents recommend greater collaboration between the

²⁴² Committee for Orphan Medicinal Products (COMP); the Committee for Medicinal Products for Human Use (CHMP); the Committee for Advanced Therapies (CAT); and the Paediatric Committee (PDCO).

²⁴³ The following bullet points are a synopsis of the COMP's discussion, which were recorded by the study team in the first instance and subsequently checked with the COMP and the Commission.

committees to improve the efficiency of procedures, especially when it comes to scientific advice. The respondents offered no practicable suggestions as to what the EMA might do in order to improve coherence at this level. However, the COMP itself made mention of the benefits of some level of joint membership of the different committees and occasional joint meetings. About half of respondents (n=18, 51%) indicated that the alignment of procedures for application, annual reporting and confirmation is 'good' or 'very good'.

Some interviewees for orphan medicine developers and their representative associations flagged what they perceive to be inconsistencies between the assessments of the COMP, PDCO and CHMP and the advice provided by the SAWP. One interviewee explained that the fact that the Paediatric Regulation requires an agreed PIP before commencing paediatric studies "is a significant disincentive for paediatric-first or paediatric-only development."²⁴⁴ It is also felt that, because the PDCO is not closely involved in the scientific advice process and there may be disagreement between the parties, development can be delayed.

9.4. Coherence with EU research initiatives and programmes

Coherence at the level of the EU refers not only to the interaction between different regulatory frameworks but also to the interplay between the EU Orphan Regulation and other EU initiatives to support development of treatments for rare diseases. Section 5.9.1 provides an overview of research programmes funded or supported by the EU that have, or include, a focus on rare disease research. This also includes the European Reference Networks, which plays a role not only in research but also in exchange of information between healthcare providers for the purpose of improving the quality of care.

Additional relevant programmes and initiatives supported by the EU are the European Research Council (ERC) grants and Marie Skłodowska-Curie Actions (MSCA), various research infrastructures (e.g. BBMRI-ERIC, the European Clinical Research Infrastructure Network ECRIN) and projects under the Innovative Medicines Initiative (IMI).²⁴⁵ In the preparation of every work

²⁴⁴ "According to Article 16 of the [Paediatric Regulation](#), PIP applications should be submitted, unless duly justified, 'not later than upon completion of the human pharmacokinetic (PK) studies', as specified in Section 5.2.3 of Part 1 of Annex 1 of Directive 2001/83/EC. [...] The timing of submission should not be later than the end of healthy subject or patient PK, which can coincide with the initial tolerability studies, or the initiation of the adult phase-II studies (proof-of-concept studies); it cannot be after initiation of pivotal trials or confirmatory (phase-III) trials." Available at: <https://www.ema.europa.eu/en/human-regulatory/research-development/paediatric-medicines/paediatric-investigation-plans/paediatric-investigation-plans-questions-answers>.

²⁴⁵ The European Research Council (ERC) is part of Horizon 2020's Excellent Science pillar and provides large, individual grants to support frontier research in any field or discipline, including science of relevance to rare diseases. The MSCA is also part of the Horizon 2020 Excellent Science pillar and provides grants to researchers – primarily but not exclusively academic – for projects carried out at similar institutions in other countries (EU and international) or other sectors (e.g. academics in industry). It is non-thematic. However, it is able to fund high quality research and innovation of relevance to rare diseases. Horizon 2020 also funds a research infrastructure programme, which is also open to proposals relevant to rare diseases.

programme, synergies between research actions and other EU initiatives, including Regulations, are discussed with relevant parties through 'interservice consultation'.²⁴⁶ Consequently, any policy actions that have relevance to the field of rare diseases and development of orphan medicines have the aim of being coherent with the EU Orphan Regulation.

Interviewed representatives from DG RTD indicated that the EU Framework Programmes for Research and Innovation take a relatively bottom-up approach to programming, particularly in the case of Horizon2020, which does not focus on specific disease areas. This means that, whilst rare disease research is in scope, the EU has limited influence over the direction of research it supports through these programmes. Nonetheless, according to a 2017 report analysing projects funded by the EU 7th Framework Programme and Horizon 2020, 55% of rare disease-related projects were funded within calls that are not specific to rare diseases but are open to research related to all types of diseases (Directorate-General for Research and Innovation (European Commission), 2017). Also, it is worth bearing in mind that even research that is not directly targeted at rare diseases may nonetheless be relevant to the field, such as research on personalised medicine or on HTA.

The interplay between these research funding programmes and the EU Orphan Regulation is not being monitored or reported on in any formal sense, through for example the preparation of an annual report on any rare disease-related actions launched or concluded in the year. The interplay was highlighted when a call was issued under Horizon2020 for Phase I/II clinical trials on rare disease therapies for which an orphan designation had been obtained. This led to a peak in the number of applications between 2014 and 2016 and was said to have greatly increased the workload of the COMP during that period. (European Commission DG Research & Innovation, n.d.) However, the COMP has not kept record of applications received or designations granted around that time that had a link to the call.

The 2017 analysis of the EU investments in research and innovation for rare diseases via the 7th Framework Programme and Horizon 2020 identified achievements in various areas, such as the launch of new clinical trials including several large-scale multinational trials, the elucidation of new disease mechanisms, and the release of new evidence-based guidelines for diagnosis

The BBMRI-ERIC operates a pan-European network of biobanks (funded through successive EU RTD Framework Programmes). The European Clinical Research Infrastructure Network ECRIN links scientific partners and networks across Europe to facilitate multinational clinical research (<https://www.ecrin.org/>).

The Innovative Medicines Initiative (IMI) is a European Technology Platform first launched in 2005 and co-funded by industry and the 6th EU RTD Framework Programme. It continues to secure funding from the EU RTD Framework Programme, with the current strategic research emphasising patient access to new treatments.

²⁴⁶ The Better Regulation Guidelines set out the basic procedure for the preparation of an Impact Assessment (IA) in the context of policy design, which includes amongst other things, the creation of an interservice group (ISG) to oversee the development of the IA and a final interservice consultation based on the staff working document, to check the coherence of the intervention with other DGs' interventions where they share common objectives. See Bullet Point 3 on page 56 of the Staff Working Document presenting the guidelines (SWD(2017) 350.

and management of rare diseases (Directorate-General for Research and Innovation (European Commission), 2017).

Whilst it was not feasible for this study to comprehensively review what funding had been involved in the development of all authorised orphan medicines, and to what extent this included public (EU) funding, interviewees from the European Commission identified the *AlphaMan* project as a clear case where EU funding had contributed to new product development.²⁴⁷ This project focused on development of an enzyme replacement therapy for a rare genetic disease called alpha-mannosidase. (The European Commission, 2015) and resulted in the authorisation of *Lamzede*, the first ever treatment for this condition.²⁴⁸

Among academic researchers that participated in the targeted survey the relation between the EU Orphan Regulation and other EU initiatives in the rare disease field appears to not be very well known. Only 11 out of 49 respondents commented on coherence between the EU Orphan Regulation and other EU policy priorities and actions, with all but one indicating that there is moderate to good coherence.

9.5. Coherence with national initiatives and policies

Whereas the previous Sections in this chapter have looked at coherence at the level of the EU and within the EMA, this Section explores how the EU Orphan Regulation aligns with related actions taken at the *national* level by Member States. The first section analyses coherence in terms of support for rare disease research, whereas the next section looks at coherence with national policies that affect access to orphan medicines.

9.5.1. Coherence with national rare disease plans

In 2009 the Employment, Social Policy, Health and Consumer Affairs Council (EPSCO) recommended the establishment of national rare disease plans (The Council of the European Union, 2009b). The **European Project for Rare Diseases National Plans Development (EURO-PLAN)**²⁴⁹, a project co-funded by the European Commission to promote and implement national rare disease plans, was created in order to facilitate the sharing of experience between countries and to link national efforts and strategy at a European level.

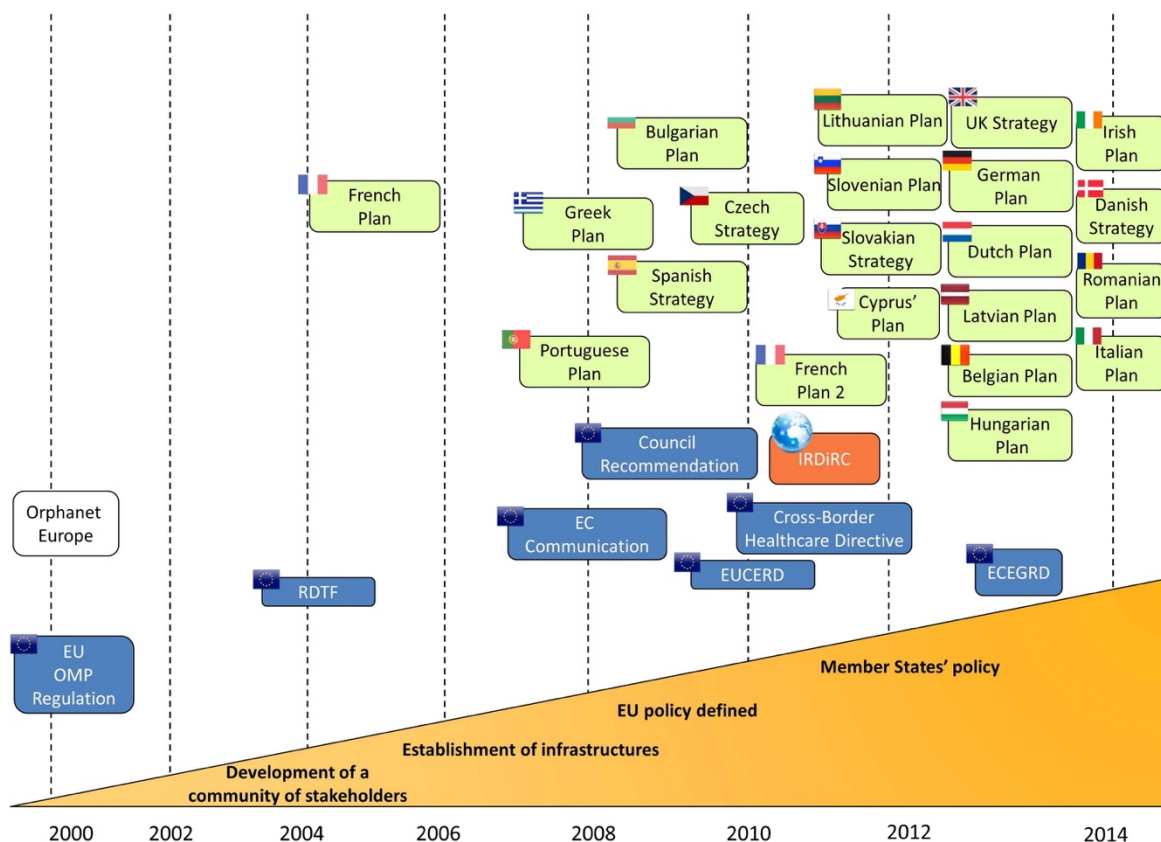
Since then, the number of Member States with a national plan has grown substantially. In 2009, only four Member States had a national plan or strategy, while in 2017 this number had increased to 23 countries. This development of Member State activities in response to the European policy actions in the period 2000-2014 is illustrated below.

²⁴⁷ The final report summary can be read online via the Commission's CORDIS research and innovation portal, <https://cordis.europa.eu/project/rcn/96911/reporting/en>

²⁴⁸ <https://www.ema.europa.eu/en/medicines/human/EPAR/lamzede>

²⁴⁹ <http://www.europlanproject.eu/Default>

Figure 36 Development of national rare disease policies



Source: C. Rodwell & S. Aymé (2015), Rare disease policies to improve care for patients in Europe. NB: Since 2014, Finland and Poland introduced their plan.

The EPSCO recommended the Member States to have their plans ready at the end of 2013. The plans were expected to pursue the following objectives (European Commission, 2017a):

- Guide and structure actions in rare diseases within national health and social systems;
- Integrate initiatives at local, regional and national levels into plans or strategies to ensure a comprehensive approach;
- Define priority actions with objectives and follow-up mechanisms.

In practice, the established plans of the Member States vary in scope and amount of financing. The main elements of the plans were:

- To organise expert care for rare diseases within the existing health systems;
- The registration of patients with rare diseases at a national level;

- The provision of information on rare diseases through support to Orphanet;²⁵⁰

It should be noted that the implementation of the plans is influenced negatively by the economic state of the past decade. Many plans have had insufficient or no funding, which limited their impact (Charlotte Rodwell & Aymé, 2015a).

In addition to having a national plan or strategy, Member States can contribute to various European and global rare disease research consortia, by participating in E-Rare²⁵¹ and the IRDiRC.²⁵²

Figure 37 gives an overview of the national plans, specific rare disease research programmes within the national plan and the participation in E-Rare and IRDiRC.

Figure 37 Characteristics of national rare disease plans and participation in E-Rare and IRDiRC²⁵³

MS	National RD Plan	Duration Plan	RD research programme	E-Rare	IRDiRC
AT	✓	2011-2018		✓	
BE	✓	2013-Undefined	✓	✓	✓
BG		2009-2013	✓		
HR	✓	2015-2020	No (outlined in NP)		
CY	✓	2012- Unknown	No (general budget)		
CZ	✓	2010- Unknown	Unknown	✓	✓
DK	✓	2014-2019			
EE	✓	2009-2020	✓		
FI	✓	2014-2017			✓

²⁵⁰ Orphanet is an online portal providing reference information on rare diseases and orphan drugs for all audiences, which was set up in France in 1997 and is now international in scope. It provides a range of services, from inventories of rare diseases and medicines through to a directory of expert resources (e.g. registries) and a collection of thematic reports. https://www.orpha.net/consor/cgi-bin/Education_AboutOrphanet.php?lng=EN

²⁵¹ The ERA-Net for Research Programmes on Rare Diseases (E-Rare) enables the pooling of resources from national and regional programmes in 17 countries - complemented by match funding from the European Commission - to expand the available funding for research on rare diseases. The network is focusing on the International Rare Diseases Research Consortium (IRDiRC) objectives (200 new therapies by 2020). <http://www.erare.eu>

²⁵² The International Rare Diseases Research Consortium (IRDiRC) promotes international (global) research collaboration. It brings together national and international governmental and non-profit funding bodies, companies (including pharmaceutical and biotech enterprises), umbrella patient advocacy organisations, and scientific researchers to promote international collaboration and advance rare diseases research worldwide. Importantly, the coverage of the Consortium is global and involves stakeholders from Africa, Asia, Australia, North America, and Europe. For more information, visit www.irdirc.org

²⁵³ Columns from left to right: Member State; Existence of a National Plan/Strategy for rare diseases; Duration of this plan; Existence of a specific rare disease research programme; Participation in E-Rare; Participation in the IRDiRC.

MS	National RD Plan	Duration Plan	RD research programme	E-Rare	IRDiRC
FR	Expired	2005-2013	✓	✓	✓
DE	✓	2013- Unknown	✓	✓	✓
GR	Expired	2008-2012	No (general budget)	✓	✓
HU	✓	2014-2020	✓	✓	
IE	✓	2014- Unknown	✓		✓
IT	✓	2013-2016	✓	✓	✓
LV	✓	2013-2020		✓	
LT	✓	2012-2017	✓		
LU	✓	2005- Unknown	✓		✓
MT		-			
NL	✓	2013- Unknown	✓	✓	✓
PL	✓	2014- Unknown	No (general budget)	✓	
PT	Expired	2008-2015	✓		
RO	✓	2014-2020			
SK	✓	2016-2020			
SI	✓	2012-2020	✓		
ES	✓	2013- Unknown	✓	✓	✓
SE		-			
UK	✓	2013-Undefined	✓		✓

Sources: RD-ACTION State of Art Reports (2014, 2016), EUROPLAN all national plans (2018), IRDiRC Member Organisations (2018), E-Rare Partners (2018)²⁵⁴

9.5.2. Coherence with national procedures for pricing and reimbursement

As all orphan medicines need to pass through the centralised procedure for marketing authorisation, one could expect that these products enter all EU markets at approximately the same time.²⁵⁵ However, as shown in Section 5.8, large variations exist in the speed with which products reach different markets or whether products enter the market at all. This relates to a significant extent to the existence of variations between the national policies for pricing and

²⁵⁴ We based our identification of national plans and research programmes on a reading of the RD-ACTION State of the Art Reports; as some of those are not available after 2014 or 2016, it is possible this account is not fully up-to-date.

²⁵⁵ See Recital 8 of Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency

reimbursement of orphan medicines (and pharmaceutical products in general). These effects can be amplified by the existence of reference pricing, as discussed in Section 6.2.2.

Based on information from stakeholder consultations, in some Member States, but not all, payers will directly follow the guidance of the EMA, as regards its scientific assessment of the benefit-risk ratio. In these cases, the granting of an EU marketing authorisation automatically means that the product is admitted into the reimbursement system, without price negotiations, at least for a limited period of time (e.g. Germany²⁵⁶)(Young et al., 2017). Other countries, like the Netherlands and the UK, indicate that they have introduced value assessments for medicines with a high (anticipated) budget impact, which affects many orphan medicines. Indeed, in many countries decision-making on reimbursement is often informed by the work of HTA agencies to establish cost-effectiveness.

The methods used for HTA may vary and outcomes are dependent on national factors, such as characteristics of the health care system and the way in which treatment with the product would be carried out (e.g. out-patient versus in-patient treatment, duration of treatment). Nonetheless, one interviewee from an HTA agency suggested that divergence in the outcomes of the value assessment more commonly resides in the opinion attached to the assessment than in the underlying assumptions and calculations. By this, it was meant that, even when different HTA agencies arrive at comparable cost-effectiveness estimates, some payers may opt to decide in favour of reimbursement whereas others will choose not to reimburse or may require price negotiations to bring down the price before a product is admitted into the reimbursement system. Value assessment is particularly challenging for rare diseases where the small populations and limited trial data tend to produce large uncertainties as regards the likely numbers of patients that might benefit and the extent of the therapeutic benefit.

As discussed also in section 6.2.2, **these differences in approaches and outcomes feed into the launch decisions made by pharmaceutical companies**, as to which orphan medicines will be brought to which market at what time. Interviews with sponsors show that these launch decisions are informed by businesses' existing knowledge about national healthcare systems and past experiences with national HTA procedures. Hence, the differences among Member States combined with pharmaceutical companies' market appraisals result in uneven access to orphan medicines. **Variability in HTA approaches across EU Member States' thus is an impediment of sorts to the full realisation of the central aim of the EU Orphan Regulation, which was intended to ensure a high level of health protection for all and ensure the same quality of treatment to patients with rare diseases.**

Differences in the outcomes of value assessment procedures, and by extension in the availability of products, are often difficult to accept for those directly

²⁵⁶ Orphan medicines are guaranteed "a positive additional benefit, as long as the value of sales at GKV expense stays below €50 million per 12 months." (Bouslouk, 2016)

affected, such as patients, carers and physicians. They observe that a treatment is available to patients in a neighbouring country but not to them. Representatives from Member States have also indicated that, once a product has been approved for reimbursement in one country, it becomes increasingly difficult for other countries to refuse or put conditions on that same product under pressure from patient advocacy organisations. **It is thus becoming increasingly important for HTA agencies to develop a common approach**, at least to parts of the assessment procedure, and to transparently communicate to the public about their reasons for not recommending reimbursement. The **European Network for Health Technology Assessment (EUNetHTA)** has been working towards this objective since its formation in 2006. It has been supporting collaboration and information exchange among Europe's HTA agencies with a view to improving the robustness and efficiency of HTAs and improving the coherence and efficiency of HTA processes.

There has been a particular interest in improving the efficiency of the interplay between EU and national actors in the area of orphan medicines, for example around the definition of unmet medical need or the similarities and differences in the concepts of 'significant benefit' and 'added therapeutic value.'²⁵⁷ There has also been substantial efforts to improve the flow of information and dialogue across the EU and national levels through, for example, early dialogue to expedite market introduction.

Despite the good progress made by current EU cooperation efforts, supported by the Commission, there are still differences in national HTA processes and methodologies that can impede market access. The **Commission's proposal for a new Regulation on HTA**²⁵⁸, which is currently under discussion in the European Parliament and the Council, aims to provide a legal framework for strengthened and sustainable EU cooperation on HTA. The proposed Regulation would enable national HTA authorities to provide joint scientific advice to medicine developers (including a possibility for advice in parallel with EMA), which would facilitate the design of clinical trials that generate appropriate evidence for both marketing authorisation and HTA. National HTA authorities would also conduct joint clinical assessments of centrally authorised new medicines (including orphan medicines). Such high-quality joint clinical assessments would support Member States in taking timely, evidence-based decisions on pricing and reimbursement and thereby contribute to the objective of timely patient access to truly innovative medicines across the EU.

²⁵⁷ See page 3 of the EMA-EUnetHTA three-year work plan 2017–2020, https://www.ema.europa.eu/en/documents/other/ema-eunetha-three-year-work-plan-2017-2020_en.pdf

²⁵⁸ Proposal for a Regulation of the European Parliament and of the Council on health technology assessment and amending Directive 2011/24/EU, COM(2018) 51 final, Brussels, 31st January 2018

The proposal refers to orphan medicines as an area where there ought to be particular benefits.²⁵⁹

Another important step to improve transparency and communication in the decision-making involving orphan medicines is the recent introduction of the '**Orphan Maintenance Assessment Report (OMAR)**' for every orphan designated medicine that has been recommended for marketing authorisation.²⁶⁰ Purpose of this report is to allow patients and companies to better understand the COMP's decision-making. Also, HTA bodies may use the information in their own processes to establish cost-effectiveness. The OMAR thus responds to a need, expressed by various stakeholders, for HTA bodies and the EMA to work together more effectively in sharing and clarifying information.

Conditional access and managed entry agreements

Some of interviews with representatives of national public authorities suggest there is growing pressure on reimbursement authorities to issue guidance on innovative medicinal products with a partial or immature evidence base.²⁶¹ This can apply particularly to orphan medicines, where there is greater uncertainty regarding the clinical and cost-effectiveness of the new technologies, which translates into a larger risk to the health-care payer and an increased likelihood that promising treatments will not be approved.

Alongside such guidance, national authorities are looking for alternative reimbursement approaches for such products, such as conditional reimbursement. For instance, in 2012 the Dutch government introduced conditional reimbursement for orphan medicines, requiring reassessment after four years on the basis of additionally collected information (College voor Zorgverzekeringen, 2012). According to representatives of the Dutch HTA body, this policy has since then been changed again and another measure was introduced for orphan medicines that are not considered cost-effective: these will be discussed in an 'indication committee', which decides on start-stop criteria and on appropriate use (Zorginstituut Nederland, 2015).

Several countries have introduced so-called 'managed entry agreements'. These agreements are used in the context of reimbursement for medicines for which the evidence base is immature. They aim to balance the need for speedy entry into the health system for treatments that address an important unmet medical need with ensuring best value for money and affordability. A 2013 comparative study of managed entry agreements in seven European countries showed that these agreements are being used increasingly across the EU, mostly for oncological medicines (Morel et al., 2013).

²⁵⁹ See bullet point 3 of Section 1.4.3 of the Commission's proposal for an HTA Regulation (p42, COM(2018) 51), Expected Results and Impacts.

²⁶⁰ <https://www.ema.europa.eu/en/news/orphan-medicine-still-orphan-once-it-gets-market>

²⁶¹ For example, in April 2017, the UK national HTA agency, NICE, issued 'highly specialised technologies (HST) guidance' for new medicinal products for very rare conditions. <https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-highly-specialised-technologies-guidance>

Also the EU Expert Panel on effective ways of investing in Health singled out orphan medicines as a particularly important area where novel payment methods need to be considered.²⁶² The panel sees a need for further development of HTA methodologies in order to secure the full benefit of the various EU Regulations designed to incentivise increased private investment in orphan products.

The EMA has also felt the pressure to accelerate access to promising, but not (yet) fully proven, treatments. This had led to the Adaptive Pathways pilot that was discussed in Section 6.3.2.

9.6. Concluding remarks on coherence of the EU Orphan Regulation

This Section brings together the main findings on the four evaluation questions that were posed in connection to coherence of the EU Orphan Regulation.

Coherence and complementarity with other EU and national interventions in the pharmaceutical area

Our study indicates that the EU Orphan Regulation is externally coherent with other interventions that have similar objectives. We find a good degree of complementarity among related pieces of legislation, at least in terms of their objectives, with evident cross-referencing of the EU Orphan Regulation to other key legal texts. There are clear links with the Paediatric Regulation (1901/2006/EC), the ATMP Regulation (1394/2007/EC), and the Regulation concerning SPCs for medicinal products (469/2009/EC). The EU Orphan Regulation's objectives also align with that of other EU policies relating to the pharmaceutical sector, as exemplified by the Regulation's focus on encouraging additional investment in R&D and the European Commission's wider commitment to support innovation and competitiveness in this strategic sector.²⁶³ Stakeholders from industry, for the most part, view the different EU policy actions as complementary, each serving a distinct purpose. It is this system of protections and incentives as a whole that, according to industry representatives, creates an environment in which pharmaceutical innovation is stimulated.

This, however, does not mean that the different regulations and policies all work together to optimal effect. This is most apparent in the interplay between the EU Orphan Regulation and the Paediatric Regulation. Our analysis has indicated that there is insufficient development of treatments for children with rare diseases, and that the two Regulations that should cater for this population apparently do not offer the necessary incentives to steer this.

More generally, it has been noted that the overall regulatory system for pharmaceutical products in the EU is rather complex and would benefit from a more holistic and streamlined architecture. The complexity is seen, for instance, in the use of apparently similar yet distinct concepts (for example, "significant

²⁶² See p. 23 of Innovative Payment Models for High-Cost Innovative Medicines, Report of the Expert Panel on effective ways of investing in Health (EXPH), Luxembourg, January 2018

²⁶³ See the Commission Staff Working Document: "Pharmaceutical Industry: A Strategic Sector for the European Economy, SWD(2014)216/F1

benefit” versus “major public health interest” or “added value”) between regulations or procedures and in how different assessment processes are organised with respect to each other.

Stakeholders from, in particular, national public authorities also expressed some concerns about the fact that, for some orphan medicines, sponsors have the ability to ‘switch’ between the protections offered by the EU Orphan Regulation and the Paediatric Regulation (i.e. orphan market exclusivity and paediatric SPC extension, respectively). This creates uncertainty for generics manufacturers about the exact term of the protection, which can further delay the entry of competition into the market.

The EU Orphan Regulation has played an important role in encouraging the implementation of various complementary, non-legislative EU initiatives. The European Commission has been active throughout the study period (2000-2017) in supporting the expansion in the investment in rare disease research and creating pan-European networks of researchers, infrastructures and registries. The EU Orphan Regulation creates the policy framework to support development of orphan medicines, whilst other EU actions support the infrastructure in which pharmaceutical R&D takes place.

There are good links between the EMA and the national health authorities and HTA agencies. These parties are aligned in their objectives to provide patients with rare diseases the necessary treatments, recognising the role played therein by the pharmaceutical industry. Nonetheless, stakeholders from different interest groups (e.g. sponsors, national public authorities, patient organisations) have expressed concerns about the apparent lack of coherence between national policies for decision making on pricing and reimbursement of orphan medicines, which is contributing to variations in access throughout the EU/EEA. The current Commission proposal for a new EU Regulation on HTA, if adopted, may be a necessary next step to achieve a higher level of convergence in HTA methodologies and greater coherence between the EU procedures for marketing authorisation and national procedures for medicines reimbursement.

Internal coherence between the tools of the Orphan Regulation

Our research has found the EU Orphan Regulation to be internally coherent, with a good interplay between its different structures and procedures. It offers a set of incentives that work well together and are of relevance to both smaller and larger developers.

Each of the tools or incentives that is part of the EU Orphan Regulation has its own objectives and value and addresses distinct needs across the product development lifecycle. These range from the award of market exclusivity to reduce the risk of developing orphan medicines to the support for public R&D as a means by which to expand the rare disease product pipeline. The fee waivers and protocol assistance further improve the balance of risk and reward for private actors and are particularly important to smaller enterprises and sponsors of more innovative therapies. Sponsors appreciate the various tools and find that there is generally good coherence between them.

Our consultations and interviews also suggest the various EMA committees cooperate reasonably well together with some level of common membership, published timetables and ad hoc joint meetings. Nonetheless, the view of the

COMP is that there is some room for improvement in, for example, the alignment of internal processes within the EMA, such as between the SAWP and PDCO. The time line associated with decision making is also different for both CHMP and COMP. This requires some consideration (possibility for COMP opinion after CHMP opinion to allow time for the scientific discussion at COMP once the final therapeutic indication has been defined), which has apparently caused issues in the past.

Linkages between orphan and paediatric medicines

As around 50% of all rare diseases manifest in childhood, there is a clear need for the development of orphan medicines for paediatric indications. It is therefore appropriate that there is an explicit link between the EU Orphan Regulation and the Paediatric Regulation, in the form of an extension of the period of market exclusivity for orphan medicines for which paediatric investigations were completed. Nonetheless, our analysis shows that only half of all currently authorised orphan medicines have been approved for use in children.

As mentioned before, this lack of development of treatments for children with rare diseases may relate, at least in part, to the fact that – even together – the Orphan Regulation and Paediatric Regulation do not provide the necessary stimuli to direct developers towards this important area. The sub-optimal interaction between the Regulations can be seen, for instance, in how conditions are defined. Normally, the EU Orphan Regulation framework will aim to define conditions as broad as possible to include all potential therapeutic indications. The tendency is then to consider both adult and paediatric populations together.

However, this approach could mean the product is not eligible for orphan designation even though the sub-set represented by the paediatric population alone would be. Only if the paediatric sub-set is approved as an orphan indication can the EU Orphan Regulation provide the necessary incentives (including extension of the market exclusivity upon completion of the paediatric investigations). If this does not occur, the Paediatric Regulation still mandates the conduct of paediatric investigations and will reward the completion thereof. However, it does not specifically incentivise or reward successful development for paediatric application.

One particular area of concern that was felt to possibly impede the development of medicines for paediatric patients was in the consideration of waivers from paediatric investigations. Specifically, the concern expressed is that a waiver may be issued when the condition for which the medicine is being developed does not affect children, even if that medicine potentially has broader application and could be developed for conditions affecting children as well. This applies particularly in the field of oncology.

Consistency between the concepts of designation and marketing authorisation

There are various points at which it can be argued there is inconsistency between the concepts of orphan designation and the marketing authorisation for orphan medicines. For one, only a small share of designations is eventually converted into authorised products. This may unduly raise the expectations of patients with conditions for which products have been designated, but where

none are successfully developed. This is, however, no different from other areas of product development.

Some measure of inconsistency also exists between the application of the concepts of orphan indication, which is used for designations, and therapeutic indication, which describes for whom an authorised treatment can be used. Here too, though, it is not clear that this poses a real problem even though it could potentially be confusing in public debate around the EU Orphan Regulation.

10. EU added value

The EU Better Regulation guidelines for evaluation define **EU added value** as follows:

EU added value

EU-added value looks for changes, which it can reasonably be argued, are due to the EU intervention, over and above what could reasonably have been expected from national actions by the Member States.

Source: Better Regulation Toolbox, #Tool 47.

In the context of this study, EU added value refers to the extent to which changes observed in the functioning of the orphan pharmaceutical system across the EU can be attributed to the EU Orphan Regulation and are additional to what could have resulted from interventions initiated at regional or national levels by both public authorities and the private sector.

Specifically, the study team has addressed two evaluation questions in the context of EU added value:

- What has been the added value resulting from EU intervention in the Orphan Regulation compared to what could be achieved at international, national or regional level without such intervention?
- What is the value of non-legislative initiatives in the field of rare diseases (registries, information/epidemiological databases, etc.) for the proper functioning of the Orphan Regulation?

Ideally, establishing EU added value, would be done by comparison against a counterfactual scenario in which the EU Orphan Regulation was not implemented. Such a counterfactual could, for instance, be based on another region that is similar to the EU in important characteristics (such as pharmaceutical R&D intensity, patient population, and purchasing power) but which has not introduced specific legislation to incentivise development of new orphan medicines. However, as regions like the US, Japan and Australia have all introduced broadly analogous policies, there is no candidate comparator or source of data on which to construct such a counterfactual situation.

In the absence of a proper counterfactual, our work to explore and quantify the extent of EU added value has relied on desk research, specifically the comparison with the situation in the EU prior to the introduction of the Regulation in 2000 described in Section 2.2, and on the comparator analysis described previously in Section 7.3. These analyses were complemented by the feedback from our interviews and surveys, that describe the relation between the incentives provided by the EU Orphan Regulation on the one hand, and outcomes, which are over and above what, could reasonably have been expected from national actions by Member States on the other.

After recapping the main findings from the comparator analysis in relation to the baseline situation (Section 10.1), the next sections address the overarching principles of subsidiarity (Section 10.2) and proportionality (Section 10.3). This is followed by a reflection on the added value offered beyond that of other

initiatives, legislative (Section 10.4) and non-legislative (Section 10.5), at both the national and European levels.

10.1. EU added value compared to the baseline situation

Ultimately, the question of whether the EU Orphan Regulation has brought EU added value rests on whether the results achieved exceed those which could realistically have been expected without the Regulation, whether by Member States acting alone or simply leaving matters to the market and wider developments in other jurisdictions.

In qualitative terms, it is clear that Member States themselves have played an important role in furthering the field of rare disease research and in improving the quality of care for patients with rare diseases. Stakeholders from all perspectives widely agreed that the EU Orphan Regulation has acted as a catalyst and that it has contributed in ways that would not have been possible at the national level alone, even when aggregated across Member States. However, as mentioned in the introduction to this Chapter, quantifying this impact is challenged a great deal by the absence of a true counterfactual.

To determine the EU added value offered by the EU Orphan Regulation (in the period 2000-2017) over a hypothetical comparator situation in which the EU Orphan Regulation had not been introduced, various analyses were performed by comparing the situation for orphan medicines with the situation before 2000, while correcting for general trends in development and marketing of medicinal products. These analyses were discussed previously in Section 7.3. Whilst there are important limitations to these analyses, in summary, they suggest that the EU Orphan Regulation contributed to:

- Development of an additional 21 orphan medicines
- Faster introduction of orphan medicines in the EU by, on average, 9 months
- Increased availability of orphan medicines for, on average, an additional 14 million citizens.

When comparing the increased number of orphan medicines on the market against the baseline situation before 2000, the added value derived from the EU Orphan Regulation is somewhat modest. Of the 142 orphan medicines introduced onto the EU market since 2000, just 21 (15%) are estimated to be attributable to the Regulation. This compares to a baseline of between 15 and 70 treatments for rare diseases²⁶⁴ available in the EU before 2000.

These additional treatments are often of great value to patients, offering increased life-expectancy and improved quality of life. Taking into account actual sales volumes, the EU Orphan Regulation was estimated to have

²⁶⁴ As explained in Chapter 2, there is no single value that can be used as a baseline as before 2000 there was no unified definition of an orphan medicine and existing products were not (re)assessed for eligibility for orphan designation under the EU Orphan Regulation framework. The values of 15 and 70 represent the lower and upper-bounds identified on the basis of literature and availability of 'orphan-like' products, classified as orphan medicines in the US.

contributed to a gain in between 210,000 and 400,000 quality-adjusted life years for patients with rare diseases in the EU.

Importantly, though, our analyses also highlighted that, in terms of time-to-market and availability of orphan medicines, these averages obscure very substantial differences between Member States. Therefore, whilst we consider the added value of the Regulation to the EU as a whole, it is fair to say that **the value for some Member States has been well below that average**. Whilst these countries have paid into the system (through the Member State contributions to the EC and EMA), they have gotten comparatively little out of it.

It is not possible to derive for which groups of patients the EU Orphan Regulation has offered the most value. Section 5.4.1 highlights that there has been a comparatively high level of activity in development of treatments for rare cancers. Comparison against the set of 'orphan-like' products that were on the market in the EU before 2000 (Section 2.2, Figure 3) indicates that this over-representation of anti-cancer products predates the EU Orphan Regulation and that, **overall, the pattern of authorised products across therapeutic areas has remained fairly similar**. It appears that the EU Orphan Regulation, alongside other measures, has successfully raised the level of R&D activity in all main therapeutic areas.

Whilst the above observations are derived from a comparison against a hypothetical situation of 'no EU Orphan Regulation' with all other factors remaining the same (correcting for observed trends in those factors), it does allow us to establish what impacts could have been achieved against a similarly hypothetical scenario of other measures having been introduced *instead* of the EU Orphan Regulation. There are no data available that would allow such a calculation. Instead, Section 10.2 discusses in qualitative terms what other measures could have been considered and what type of impacts could have been expected from this.

10.2. Subsidiarity of EU action

In general, EU actions in areas that are not under the exclusive competence of the EU are only considered justified "if, and in so far as, the objective of the action cannot be achieved sufficiently by the Member States (at national, regional and local levels); but can rather be better achieved at Union level by reason of the scale or effects of the proposed action."²⁶⁵ This is referred to as the principle of **subsidiarity**.

In the context of supporting the development of orphan medicines through an EU Regulation, the question then is whether the Regulation offers the ability to achieve effects beyond those possible through the actions of individual Member States. Moreover, we also looked at whether specific aspects of the Regulation would have not been possible, or led to undesirable effects, would these have been implemented at a national level.

²⁶⁵ Subsidiarity. https://ec.europa.eu/info/sites/info/files/file_import/better-Regulation-toolbox-5_en_0.pdf

An EU-level approach to supporting development of orphan medicines is able to aggregate demand among the small numbers of patients affected nationally. The decision to implement the EU Orphan Regulation addressed this issue of small populations and market fragmentation directly by creating economies of scale to an extent that would not be possible through individual national policy initiatives.

In principle, a national approach to this pressing social challenge is possible, as demonstrated by legislators in the US and Japan. However, the market for individual orphan medicines is too small even amongst the larger EU member states, so any **national initiative would have needed to provide substantial incentives to cause firms to change their investment behaviour.** This would not have been allowable under the terms of the EU treaty, as this would have risked distorting the EU internal market. It would have been at odds with the Treaty's objective "to promote the completion of the internal market through the adoption of uniform regulatory decisions based on scientific criteria concerning the placing on the market and use of medicinal products". (The council of the European Communities, 1993)

The EU Orphan Regulation does not preclude 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 in fact are part of the measures offered under the regulatory frameworks for orphan medicines in the US and Japan. A 2015 study provides an overview of Regulations and policies related to orphan medicines in 35 countries, including 21 EU countries (Gammie, Lu, & Babar, 2015). It shows that tax exemptions are offered also in Belgium and France and that Spain provides reduced rebates. However, overall it appears that **few EU countries offer specific financial incentives for developers of orphan medicines.** Particularly for smaller Member States, it is unlikely that financial incentives at a level that would have made an appreciable difference on the pipeline for orphan medicines would have been feasible.

As an alternative to EU action, transnational and regional initiatives could also have been considered. For instance, the Netherlands, Belgium, Luxembourg and Austria initiated the BeNeLuxA collaboration, to which Ireland recently joined.²⁶⁶ Purpose of this collaboration is to work on, among other things, joint assessment of products and joint price negotiations with pharmaceutical companies. Another alliance of countries (by Cyprus, Greece, Ireland, Italy, Malta, Portugal, Spain, Romania, Slovenia and Croatia) has been formed in 2017 under the Valletta Declaration²⁶⁷. Neither of these collaborations though is aimed at supporting pharmaceutical development in general, nor that of orphan medicines in particular. There is no evident rationale that such smaller transnational initiatives, had they emerged, would have been more effective or efficient than EU level action.

²⁶⁶ The 4 main areas of work for BeNeLuxA are: 1) Horizon Scanning, 2), Health Technology Assessment, 3) Information sharing and policy exchange, and 4) Pricing and Reimbursement. <http://www.beneluxa.org/>.

²⁶⁷ <https://globalpricing.com/news/taking-stock-european-cross-border-cooperation-on-medicines-value-assessment-and-pricing-reimbursement-negotiations/>

The EU added value is recognised by 76% of the academic researchers and experts (32 in total) who participated in a targeted survey: they agreed or strongly agreed with a statement that, at the time the EU Orphan Regulation was introduced in 2000, there was a clear need for concerted EU action beyond the efforts of individual Member States. Representatives of patient and consumer organisations (n=9, 75%) similarly strongly agreed with this statement. Furthermore, some respondents stated that the Regulation was needed to stimulate development of orphan medicines in individual EU Member States.

More generally, the choice for a Regulation as the policy instrument can be viewed as justified, as it removed the risk of delays and variability between Member States that could have resulted if transposition into national policies had been needed.

We conclude that the introduction of the EU Orphan Regulation respected the principle of subsidiarity by introducing a measure that allowed for the achievement of aggregated effects beyond that which could realistically have been achieved by individual Member States.

10.3. Proportionality of EU action

The principle of **proportionality** means that “the content and form of Union action must not go beyond what is necessary to meet the objectives of the Treaties. Respect for the principle of proportionality is about ensuring that the policy approach and its intensity match the identified problem/objective”.²⁶⁸

The EU Orphan Regulation is a proportionate response to what is a major challenge for all European member states, with 6,000-8,000 life threatening and debilitating diseases affecting tens of millions of European citizens, many of them children. Although we did not estimate the societal cost of rare diseases in monetary terms, it is clear that the implementation cost of the Regulation (e.g. costs of staff at EMA, fee waivers and protocol assistance) is small by comparison.

As mentioned previously, the EU Orphan Regulation leaves room for individual Member States to continue to play their part in promoting the development of orphan medicines. Member States maintain the freedom to invest national funds in rare disease research. The Regulation also did not interfere with the responsibility of Member States to determine what medicines to allow entry into national reimbursement systems, nor does it encroach on the national responsibility of Member States for health care.

Numerous stakeholders have remarked on the undesirable price effects that have repeatedly been associated with authorised products that obtained an orphan designation, where the status of a product as an orphan medicine and the resulting market exclusivity are viewed as direct contributors to the price charged for the product. It could thus be argued that in the case of such products, the cost implications of the Regulation have been disproportionate in respect of its objectives. However, extrapolating this argument to the entirety of the Regulation is challenged by the fact that there are insufficient data to fully

²⁶⁸ Proportionality. https://ec.europa.eu/info/sites/info/files/file_import/better-Regulation-toolbox-5_en_0.pdf. Treaties herein refers to Article 5(4) of the Treaty on European Union.

calculate the economic value of the market exclusivity (as discussed in Section 8.3.2). Such data would be required to calculate the full costs of the Regulation.

We conclude that the absence of safeguards to protect Member States, and by extension patients with rare diseases, from excessive costs resulting from the incentives provided by the Regulation, means the Regulation risks being disproportionate in some cases.

10.4. National policy actions by Member States

Legislative efforts in the EU have focused predominantly on the development of innovative treatments for patients with rare diseases. While this is fundamental within the field of rare diseases, the EU has also taken steps to ensure comprehensive and complementary national policy programmes are in place, to address the broader needs of patients and to ensure the optimum functioning of such legislation.

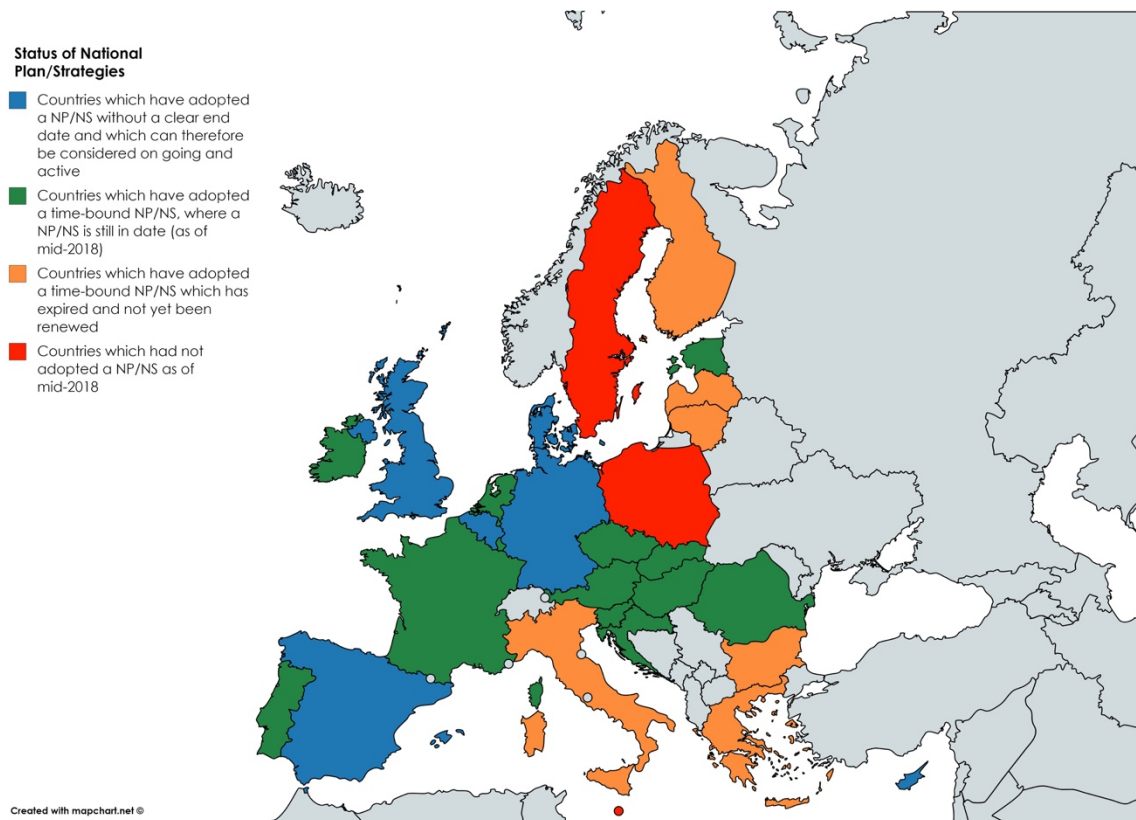
In 2009, the Council of the European Union adopted the "Recommendation on an Action in the Field of Rare Diseases," which supported and catalysed the adoption and implementation of **national plans and strategies to address the comprehensive needs of patients with rare diseases**. (The Council of the European Union, 2009c). These plans rarely put specific (national) legislation in place but do make public commitments to act and indicate the initial 'readiness' of the country to respond in the field of rare diseases and orphan medicines. This includes aspects such as improving awareness of rare diseases, support for research, development of centres of expertise, the empowerment of patient organisations and the implementation of a robust healthcare infrastructure.

As discussed in Section 9.5, while the scale and scope of the policies, plans and strategies varies from country to country (Charlotte Rodwell & Aymé, 2015b), there are a number of initiatives that have been widely taken up and which are judged as having contributed significantly to the rare disease research landscape and the improved functioning of the Orphan Regulation.²⁶⁹

Figure 38 shows the status of national plans across the EU, with a majority of Member States having adopted strategies for rare diseases that are current either with an end date that is yet to occur or an open commitment.

²⁶⁹ For a list of national plans for rare diseases, see <http://www.europlanproject.eu/NationalPlans?idMap=1>.

Figure 38 Status of national plans and strategies (mid-2018)



Source: RD Action data and policies for rare diseases²⁷⁰

Additionally, some Member States have introduced **policy initiatives to support access to orphan medicines** outside of the normal systems for reimbursement. For example, the UK's €380m Cancer Drug Fund (CDF),²⁷¹ managed through the National Institute for Health and Care Excellence (NICE), can approve – and finance – access to medicines for rare cancers where there are promising results in trials but there is insufficient evidence for a full assessment and a definitive 'yes' or 'no' decision. The treatment can then be made available selectively and will be closely monitored with the additional evidence reviewed after two years to make a final decision based on efficacy and value for money. In Belgium, sales of orphan medicines are exempt of tax (Belgian Health Care Knowledge Centre, 2009)(Gammie et al., 2015). Likewise, in France pharmaceutical companies promoting orphan medicines have been exempted from the taxes and contributions owed to the Sickness Insurance and the French national competent authority (Gammie et al., 2015).

Representatives of national public authorities identified several ways in which the EU Orphan Regulation has provided additional value beyond their national efforts. These were:

²⁷⁰ <http://www.rd-action.eu/rare-disease-policies-in-europe/>.

²⁷¹ <https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/cancer-drugs-fund>.

- By offering additional incentives to support R&D of orphan medicines
- By standardising the definition of orphan conditions
- By promoting the R&D of orphan medicines more generally through research funding.

A similar question was posed to academic researchers and experts. They mostly saw this value in the Regulation having contributed to a standardisation of the definition of orphan conditions in the EU, but this was closely followed by the impact the Regulation had on providing additional R&D incentives.

10.5. Non-legislative initiatives in the field of rare diseases

10.5.1. European initiatives to support R&D

As shown in Section 5.9.1, alongside the introduction of the EU Orphan Regulation, the EU has shown a strong commitment to rare disease research. It has done so, for instance, via the **EU Framework Programmes for Research and Innovation**, the ERA-Net for Research Programmes on Rare Diseases **E-Rare** and via its support for the **International Rare Disease Research Consortium (IRDiRC)**. Such initiatives are able to invest and bring together resources from across Europe to a degree that would be impossible at the level of an individual Member State and even a sub-set of Member States acting alone. These activities have increased the actual and effective scale of investment by the public sector in rare disease research.

Similarly, collective resources such as the European Platform for Rare Disease Registries (**EPIRARE**) and **RD-Connect** are helpful to achieve greater harmonisation and standardisation in data sharing across Europe and thus add significant value. This effect is enhanced by the creation of the **European Reference Networks (ERNs)**. Another important initiative to highlight is also the recently (2019) launched **European Platform on Rare Disease Registration** (EU RD Platform).²⁷² This platform is intended to make rare disease registries' data searchable and findable, thereby increasing their utility.

Together, these initiatives support the objectives of the EU Orphan Regulation and capitalise on the synergy that comes from working across national boundaries.

10.5.2. National initiatives to support R&D

Survey respondents were asked what main national initiatives exist in their respective countries to fund or otherwise stimulate R&D relating to orphan medicines. Researchers most frequently mentioned networking initiatives, the launch of large research programmes in the area of rare diseases and government research grants.

When asked to specify what initiatives have been taken at national or regional level in their countries that are complementary to the EU Orphan Regulation the following were mentioned: national or regional government research grants for rare diseases, a few national research centres, the creation of the national plan

²⁷² <https://eu-rd-platform.jrc.ec.europa.eu/aim-of-the-platform>

on rare disease management and the launch and/or expansion of clinical networks.

Appendix G contains an overview of **national initiatives** to support R&D for rare diseases and the development of orphan medicines. These initiatives **complement the above discussed EU programmes. It is, however, not always clear if and how these relate to European R&D initiatives or to the EU Orphan Regulation.** By this we mean that it is not clear, for instance, if EU orphan designation is a prerequisite for funding eligibility or if national research funding programmes share certain objectives or priorities with EU funding programmes. Nor is it known if national funding programmes displace contributions to EU funding programmes or vice versa. **Whilst the value of national funding programmes for rare diseases is self-evident, based on available data, it cannot be determined to what extent this value is additive to EU-level efforts.** Such an analysis is also beyond the scope of the present study.

While there has been an evident increase in the commitment to research on rare diseases, triggered in part by the EU Orphan Regulation, there are still many millions of Europeans living with rare diseases for which no treatment yet exists and where limitations in research funding and research translation may act as a brake on the Regulation's ambitions.

10.6. Concluding remarks

This section summarises key findings regarding the EU added value offered by the EU Orphan Regulation.

Added value compared to what could be achieved at international, national or regional level

The value offered by the EU Orphan Regulation above and beyond similar Regulations in other jurisdictions, in particular the US, as well as beyond national level efforts is difficult to establish. The reason for this is that this requires projecting a situation that has not taken place. Nevertheless, we have made attempted to estimate this added value against a comparator situation without the Regulation and by relating this to the baseline situation before 2000.

This study finds that the EU Orphan Regulation has contributed to an increase in the number of orphan medicines that have been developed and that are brought to market in the EU. Whilst the analysis itself is based on a number of assumptions and there is substantial uncertainty in the estimate provided, the EU Orphan Regulation is thought to have led to around 21 additional orphan medicines. This impact has occurred alongside somewhat faster access to EU markets (on average 9 months) and a slight increase in the number of EU markets where products are available (on average 0.3 Member States). Whilst all these effects are, on average, positive, there is no equity among Member States in how these benefits have been distributed.

As the results are based on statistical analysis and no individual products can be identified that could be linked entirely to the EU Orphan Regulation, it is not possible to conclude which groups of patients have benefitted most directly from the EU Orphan Regulation. Comparison against the baseline situation shows no

major trend breaks in the allocation over therapeutic areas, though this conclusion is complicated by the very low numbers of products in some areas.

Overall, it is reasonable to state that the EU Orphan Regulation has allowed for a more concerted and effective response to the challenge of market failure in the development of orphan medicines than would have been possible at the level of the individual Member States alone. It has also acted as a catalyst to the efforts made by the Member States in the field of rare diseases and orphan medicines. The market exclusivity offered to EU authorised orphan medicines has been identified as one of the key incentives offered by the Regulation. This would not have been possible at the level of an individual Member State, as it would have led to distortions of the internal market.

Value of non-legislative initiatives in the field of rare diseases

Our findings suggest that, as regards cooperation and research funding, substantial added value has been brought by the efforts of the EU in the space of rare diseases and orphan medicines. The EU contributes to a wide variety of non-legislative initiatives. These initiatives offer substantial added value by bringing together stakeholders and bundling expertise and data. As such, they complement the EU Orphan Regulation by strengthening the field of rare diseases research and orphan medicine development.

11. Concluding remarks

This study finds that the EU Orphan Regulation has contributed to important strides in the field of rare diseases and development of orphan medicines. Since the Regulation was introduced more products have come on the market. There is also a promising pipeline of products under development that may bring real value to patients for whom currently no treatment options exist. Additionally, products are reaching patients faster and are reaching a somewhat greater number of EU markets. Yet, the goals of the EU Orphan Regulation are far from fulfilled: for the majority of rare diseases there remain no good treatment options. As such, the objectives of the Regulation remain as important today as they were nearly two decades ago.

Notwithstanding these important successes, this study has shown that progress has not been even in all areas. The EU Orphan Regulation has also produced some unintended effects that in 2000 were either not foreseen, or for which the magnitude of their impact was not adequately predicted. It is therefore timely to consider various aspects of the regulatory framework for orphan medicines in the EU. However, it is important to bear in mind that any modifications to the regulatory framework, particularly to the instrument of market exclusivity, solely for the purpose of better bringing in line costs and rewards could have the undesirable 'side-effect' of also slowing down much needed innovation. It is nonetheless worth considering whether and where other forms of incentives could be as effective, or more so in stimulating research and product development for rare diseases.

The present study was not tasked with drawing up recommendations or preparing policy options for the future of the EU Orphan Regulation. Instead, its focus was retrospective, whilst identifying areas of tension that could impact the Regulation in future. Where stakeholders offered up specific recommendations or points for consideration, these have been included in the report.

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Appendix A Literature review

To support the various activities of this study a comprehensive review of peer-reviewed and grey literature was conducted. The methodology followed for this is based on that of systematic literature reviews such as those performed by the Cochrane Collaboration. A detailed search strategy was developed, using key words, Medical Subject Headings (also known as 'MeSH terms') or Index terms that were combined into search strings. A screening of the thus retrieved information was performed by two independent researchers who reviewed, respectively, publication titles, abstracts (where available) and full texts. The screening was based on predetermined selection criteria. Only when the full text was deemed to meet the inclusion criteria by both reviewers (or, in case of disagreement, after review by a third assessor) were articles included.

The next Sections outline which sources and search strategies were used, and how the retrieved literature was selected and analysed.

A1. Literature selection and screening

For peer-reviewed literature, the following data sources were searched:

- PubMed (including MEDLINE)
- Scopus
- The Cochrane Library.

Two separate search strategies were used: one to cover the orphan medicinal product landscape globally and another to identify literature related to the impact of orphan medicinal product Regulations in the geographies of interest (WP2, 4 and 5). For the first, no restrictions were posed on geography, intervention or impact area. Hence, for PubMed the search string was:

1. ("Rare diseases"[MeSH] OR "rare disease*"[TiAb] OR "rare condition*"[TiAb] OR "orphan disease*"[TiAb] OR "orphan condition*"[TiAb] OR "orphan drug"[MeSH] OR "orphan medicine"[TiAb] OR "orphan medicinal product"[TiAb]);

AND

2. (Regulation[TiAb] OR Polic*[TiAb] OR legislation[TiAb] OR incentive*[TiAb] OR approval[TiAb] OR program*[TiAb] OR initiative[TiAb] OR investment*[TiAb] OR "drug discovery"[MeSH] OR development[TiAb] OR R&D[TiAb] OR access[TiAb] OR availability[TiAb] OR market[TiAb]).

For the second search string, the following was used:

1. ("Rare diseases"[MeSH] OR "rare disease*"[TiAb] OR "rare condition*"[TiAb] OR "orphan disease*"[TiAb] OR "orphan condition*"[TiAb] OR "orphan drug"[TiAb] OR "orphan medicine"[TiAb] OR "orphan medicinal product"[TiAb]);

AND

2. (Regulation[TiAb] OR Polic*[TiAb] OR Act[TiAb] OR legislation[TiAb] OR incentive*[TiAb] OR "orphan designation"[TiAb] OR "orphan drug status"[TiAb] OR approval[TiAb] OR program*[TiAb] OR initiative[TiAb] OR investment*[TiAb] OR support[TiAb] OR "market exclusivity"[TiAb] OR monopoly[TiAb] OR reward*[TiAb]);

AND

3. (cost[TiAb] OR pric*[TiAb] OR expenditure [TiAb] OR affordability*[TiAb] OR benefit[TiAb] OR value[TiAb] OR impact[TiAb] OR effect[TiAb] OR sustainability[TiAb] OR reimburs* OR "technology assessment, biomedical"[MeSH] OR "economic assessment"[TiAb] OR access[TiAb] OR availability[TiAb] OR coverage[TiAb]);

AND

4. (Europe OR "European Union"[MeSH] OR "European Union" OR EU OR "European Medicines Agency" OR EMA OR "United States"[MeSH] OR "United States" OR USA OR "united states food and drug administration"[MeSH] OR "united states food and drug administration" OR FDA OR Japan OR Australia).

Similar searches were created for other databases. Additionally, the reference lists of included studies were reviewed for other potentially relevant publications.

Grey literature (i.e. literature that has been published outside of traditional commercial channels or academic publishing channels, such as government or business reports, policy documents, theses or conference presentations) was retrieved from the websites of the European Commission (DG RTD and DG SANTE, European Medicines Agency, EFPIA, EuropaBIO, EURORDIS, FDA, OrphaNet, PMDA (Japan), and TGA (Australia).

Additional searches of both peer-reviewed and grey literature were run using Google Scholar.

A2. Screening of literature

At every stage of the process, two consultants independently assessed publications for their relevance and adherence to inclusion criteria based on the title of the publication. Any title judged as potentially relevant by either of the assessors was retained for further scrutiny in the next stage of the selection process. Next, potentially eligible publications were screened on the basis of abstracts. When no abstract was available, the publication was retained until the next stage of screening.

A3. Data extraction and reporting of findings

For each publication that was deemed eligible for inclusion, keywords related to topics covered by evaluation questions were assigned to allow the selected publications to be split for separate syntheses. Full-text publications for each topic were read and included or excluded based on the relevance of the content

i.e. whether there was information that would help answer an evaluation question. Data extraction and reporting was done simultaneously and thematically with a view to providing information on the landscape and state of the art, while also putting the findings into context and discussing the implications for policy and practice.

Appendix B Portfolio analysis

The portfolio analysis included in this report is based on analysis of the data received from EMA and IQVIA. This comprehensive set of data was cleaned (i.e. remove apparent data entry errors), restructured and linked to ensure that we could run our proposed analyses.

The table below provides an overview of the variables that appeared in the portfolio dataset:

Variable	Explanation
Status	
Designated	OMP which has received a designation
Expired OD/Market exclusivity period	Market exclusivity period of orphan medicine expired
Negative EC designations	OMP received a negative EC decision on its designation application
Withdrawn designations EU registry	OMP which had received a designation is withdrawn from the EU registry
EMENumber	EMA reference ID
UPINumber	EMA unique reference ID
Sponsor	Name of the sponsor
Country	Country of the sponsor
Active substance	Substance responsible for the activity of a medicine
Orphan indication	Indication on which sponsor applies for a designation
ATCCode	A system of alphanumeric codes developed by the WHO for the classification of drugs and other medical products
Start Date OD	Date at which EMA starts the process of submitted designation
Submission Date OD	Date at which sponsor submitted request for OD
Opinion Date OD	Date at which COMP finalises/communicates its opinion
Opinion Type OD	
Positive	OMP receives a positive opinion on orphan designation
Negative	OMP receives a negative opinion on orphan designation
Decision Date OD	Date at which Commission adopts decision
Decision Number OD	EU reference ID
Prevalence at the time of designation	Prevalence of value/10.000
IsPaediatric	Indication is prevalent in children
IsAdult	Indication is prevalent in adults
Withdrawal date	Date at which an orphan medicine in the process of attaining a designation withdraws their application
Tradename	Name of orphan medicine given by sponsor
Therapeutic Indication	Therapeutic indications are a description of the disease to be treated with a medicine. This is narrower than the orphan indication provided at time of designation
MAA Start date	Date at which an designated orphan medicine enters procedure for Marketing authorisation

Variable	Explanation
MAA Opinion date	Date at which EC finalises its opinion for Marketing authorisation
MAA Authorisation Date	Date at which Marketing authorisation comes into effect
Authorised (Initial marketing authorisation application)	
TRUE	OMP does receive Marketing authorisation
FALSE	OMP does not receive Marketing authorisation
Authorised Extensions of indication	
TRUE	OMP receives extra indication
FALSE	OMP does not receive extra indication

The following Sections outline the actions that were taken to further process and analyse this data.

B1. Data cleaning and restructuring

Because most of the data points in the dataset from the EMA are entered manually, we found inconsistencies (e.g. spelling variations, typos, use of different systems for nomenclature) in the descriptions of conditions, therapeutic indications, ATC codes and active substances. Where clearly visible, such inconsistencies were manually corrected.

The resulting main data set was structured according to the orphan designation, consequentially 'fitting' multiple active substances. As the database is maintained at the level of the designation, there is no immediate identifier that will highlight unique active substances that are developed. For that purpose, we have constructed an identifier, to understand how many orphan medicinal products have been awarded an orphan designation or marketing authorisation. We have done so by taking the unique active substances and created an identifier including the active substance, the sponsor and the designation date.

B2. Data categorization

Several of the variables necessary to conduct the required analyses were not present in the data set provided by the EMA. Therefore, these variables had to be created by the study team. Specifically, the variables created were:

- Type of sponsor
- Origin of sponsor
- Type of product.

B2.1. Classification of sponsor types

We have classified the sponsors to compare the composition of different types of sponsors at the time of orphan designation to marketing authorisation. We have started this process by matching a list of sponsors to the SME Register of the EMA. The EMA does not use standardized nomenclature for companies. Therefore, the same company can be listed on the SME register and on the community register of orphan medicines under different variations of the name. Such variations can occur either because in some cases abbreviations were used

(Ltd versus Limited), punctuation may have been added or not (B.V. versus BV), or because the company operates under different subsidiary names. Character matching was used to identify the closest possible fit for a sponsor name to an entry on the SME register. Matches were manually checked to verify these referred to the same company.

Once it was established which sponsors could be matched to the SME register, a further categorisation of all sponsors was performed. All entries containing the stems -univer* or -institut* were classified as an academic institution or research institute. Entries that were recognizable as personal names were classified as individuals. Those entries that contained the word 'consulting', 'consultancy' or 'advice' were classified as consultancies (potentially sub-categorised as SME consultancy if a match was found to the SME register). Unless we had reason to assume, otherwise, remaining entries were considered to be non-SME pharmaceutical or biotechnology companies. No distinction was made on the basis of whether a company performed R&D.

Overall, the following classifications and definitions were used.

Figure 39 Definitions of sponsor types

Sponsor type	Definition
Individual	An individual listed without any attribution to a company, university or research facility.
SME	A company with fewer than 250 employees or a turnover smaller than €50m and listed on the EMA SME Register.
SME consultancy	Within the broader category of SME we identified small SME consultancy business as a separate category.
Consultancy	Consultancy with more than 250 employees or a turnover of more than €50 mln.
Academic	A research institute, university or other type of publicly funded research organisation.
Pharma	A biotech or pharmaceutical company with more than 250 employees or a turnover of more than €50 mln.

B2.2. Classification by origin of sponsor

As the EU Orphan Regulation requires sponsors to be established in the EU/EEA, companies that are not based there would apply for designation either through an EU/EEA subsidiary or via an intermediary (e.g. a regulatory consulting firm). Consequently, the register contains only sponsors that are listed as being based in the EU/EEA even when the R&D activity is conducted elsewhere. Whilst imperfect, an attempt was made to better understand where companies that receive support under the EU Orphan Regulation are truly based and where (part of) the R&D may be conducted. Here to, an online hand search was conducted for all sponsors to establish where their corporate headquarters are located. There is substantial noise in this classification, as it is not always clear when a subsidiary should be considered as independently operating from the

headquarters. Therefore, the classification should be considered as approximate only.

The classification performed distinguished between the following regions: 1) EU/EEA, 2) Europe, non EU/EEA, 3) USA, 4) Canada, 5) Japan, 6) China, 7) India, 8) Australia, and 9) All other.

B2.3. Classification by type of product

Products that, based on the information provided regarding the active substance, were identifiable as proteins (e.g. containing suffixes such as *-ase*, or *-mab* or key words such as *protein*, *antibody* or *immunoglobulin* or *recombinant*), and those that were listed as 'protein based therapies' on <http://www.drugbank.ca> were all classified as **biological**, unless information was available that products were synthetic in origin.

Fusion products that were produced at least in part through a biological process were also considered biological. Additionally, cell extracts and whole cell cultures were included. Polypeptides less than 40 amino acids in size were all classified as small molecules. Whilst the general classification approach was discussed with the EMA, the classification of individual products was not independently validated by the EMA or other scientific experts.

Products were classified as **advanced therapy medicinal product** (ATMP) if the field containing the active substance included any of the words *adeno-*, *cell*, *gene*, *immunotherapy*, *plasmid*, *tissue vector*, or *viral*, unless there were clear reasons to do otherwise. The classification extends to products designated before 2008, when the EMA first officially introduced the ATMP classification.

All other products were classified as **small molecules**.

B3. Calculations

The majority of analyses are based on direct counts (either as absolutes or as percentages) of products listed in the main data set, using the applicable variables. Additionally, however, several calculations were performed that made use of additional data sets or that were underpinned by certain assumptions. These calculations are here further explained.

B3.1. Total patient population size in the EU for authorised orphan medicines

To gain insight into the potential reach of the Regulation, as well as understanding the landscape in which the Regulation is situated, we calculated the potential patient population size in Europe. We took into the number of unique conditions for which an orphan medicine had been authorised at some point in time; even though it may have been withdrawn later. This led to a subset of 110 unique orphan conditions, each specifying a certain prevalence rate as X/10.000.

Next, we extracted data on the EU population size from the Eurobarometer to match the population size to the year of the most recent designation and thus most recent prevalence rate. We then applied the following formula to attain the potential patient population in the EU per designation: prevalence rate of

designation (most recent year) * population size of the EU (the year of recorded prevalence rate)/10,000.

B3.2. Share of on-patent medicinal products among orphan medicines

To assess the extent of 'overlap' between intellectual property rights and other regulatory protections on authorised orphan medicines, we used data from MPA Business Services, which was linked to the data of the EMA. MPA Business Services looked into any major patents and/or SPCs that were on the active substance prior to, during and post the marketing authorisation. This was compiled into a dataset of 105 orphan medicines for which they were able to trace patents and/or SPCs. We excluded patents on formulation and/or process. As a reference for protection in the EU, we selected four countries to check if they had any protections on the active substance. These four countries were Germany, France, UK and Italy. Although not watertight, it was deemed a reasonable assumption that, if there would be a patent on the active substance, it would probably be encountered in at least one of these four countries.

B3.3. Allocation of designated and authorised orphan medicines by therapeutic area

To calculate the mean prevalence for conditions covered by all designations and by authorised orphan medicines, products were grouped by the main level ATC code. Then, a regular division was done of the sum of the prevalence by the frequency of designations/OMPs.

Appendix C Interviews

A list of stakeholders to be consulted via interviews was agreed between the study team and the client. Due to unavailability of certain interviewees, or unwillingness to participate, the list was amended several times throughout the study. Additionally, some of the contacted persons identified others as more relevant to the study. The final list of interviewees who participated in the study is presented in hereafter. In total, 35 separate interviews have been completed. The list presented here has been anonymised to protect the privacy of the interviewees. Therefore, only the organisations to which they are attached are listed here. However, it should be emphasised that some interviewees spoke on a personal title and that their opinions do not necessarily reflect those of the organisations listed here.

Interviews were semi-structured in nature. Interview protocols were designed for different stakeholder groups. Upon request, these protocols were sent to the interviewees in advance of the interview. Interviews were mostly conducted over the phone, with a few conducted in person. They generally lasted between 45 and 60 minutes. In some cases, interviews were held as group interviews with a number of participants. Detailed notes were taken for all interviews.

Interviewees were presented with a copy of these notes and were offered the possibility to review and, where necessary, amend these. Such amended versions were taken as leading in the analysis. When no response was received, the original notes were used.

All notes were coded using the qualitative analysis software package Atlas.ti to allow standardised retrieval of information.

In addition to having been incorporated into the analytical chapters of this report (Chapters 6 to 10), interview findings have been presented more comprehensively in a separate synopsis report, accompanying this report.

Figure 40 Overview of interviewees

Organisation	
	European Commission and executive agencies
1	Directorate-General for Health and Food Safety (DG SANTE)
2	Directorate-General for Research and Innovation (DG RTD)
3	European Medicines Agency (EMA)
	National representatives of public authorities
4	Medical Products Agency, Sweden
5	Dental and Pharmaceutical Benefits Agency (TLV), Sweden
6	Regional health board of Stockholm, Sweden
7	Federal Institute for Drugs and Medical Devices (BfArM), Germany
8	Agence Nationale de sécurité du médicament et des produits de santé (ANMS), France
9	Instituto Superiore di Sanita, Italy
10	Care Institute Netherlands (ZIN), the Netherlands
11	Ministry of Health, Welfare and Sports, the Netherlands
12	Medicines Evaluation Board (CBG/MEB), the Netherlands
13	Universitatea de Medicină și Farmacie "Carol Davila" Bucharest, Romania
14	National Agency for Medicines and Medical Devices, Romania
15	Instytut Pomnik-Centrum Zdrowia Dziecka, Poland
16	Medical University of Vienna, Austria
17	Medicines and Healthcare products Regulatory Agency (MHRA), United Kingdom
18	Spanish Agency of Medicines and Medical Devices (AEMPS), Spain
	Professional associations
19	Members of Common Group on Rare Diseases, EFPIA / EuropaBIO
20	EUCOPE
21	Medicines for Europe
	Representatives of (potential) sponsors of orphan medicines
22	Shire Pharmaceuticals
23	TIGEM
24	CIBERER
25	Novartis Europharm
26	Merck KGaA
	Patient and advocacy organisations
27	European Public Health Alliance
28	United Parent Projects Muscular Dystrophy (UPPMD)
29	European Gaucher Alliance
30	EURORDIS
	Academic researchers and experts
31	INSERM (formerly)
32	The European Society for Paediatric Oncology (SIOPE)

Organisation	
33	National Centre for Pharmacoeconomics, Ireland
	Other
34	FDA Office of Orphan Products Development, United States of America
35	Pharmaceuticals and Medical Devices Agency (PMDA) Japan

Additionally, in November 2018, two members of the study team attended part of a meeting of the COMP. This allowed them to directly observe some of the procedures of the COMP.

Study findings were presented for discussion and validation at two separate meetings: on 21 February 2019 during a meeting of the COMP and on 1 April 2019 at a meeting of the Pharmaceutical Committee with national representatives of Member States.

Unsolicited written commentary was received also from the Heads of Medicines Agencies Permanent Secretariat (HMA), the European Consumer Organisation (BEUC), and the German Pharmaceutical Industry Association (BPI).

Appendix D Targeted surveys

Initially, a total of three targeted surveys had been envisaged. During the inception phase, it was realised that, given the variety of stakeholder groups to be consulted, this would need to be extended to five separate surveys targeted respectively at representatives of:

- National public authorities;
- Developers of innovative orphan medicinal products (and their representative associations);
- Producers of generic and biosimilar versions of orphan medicinal products (and their representative associations);
- Academic researchers and experts;
- Patient and consumer organisations.

Draft versions for each of these five surveys were prepared. A first round of revisions was then made based on the feedback received from DG SANTE and other members of the Project Steering Group. These revised versions were subsequently used for pilot testing with a limited number of representatives of each of the target groups. These representatives were asked to provide feedback on the clarity of the questions, but also on the feasibility and appropriateness of the questions. They were also given the opportunity to indicate if they felt any questions were missing that they considered of importance. Figure 41 shows for each survey, which parties, provided feedback on the piloted versions.

Figure 41 Feedback received on the pilot of the survey

Version	Feedback received from
National Public Authorities	Austrian Ministry of Health (Katharina Leitner) EUnetHTA (various; consolidated feedback)
Innovative orphan medicine developers	EUCOPE (Alnylam, Biomarín, Shire; consolidated feedback) EFPIA/EuropaBIO (Pfizer, Sanofi; consolidated feedback)
Generic / biosimilar orphan medicine producers	Medicines for Europe
Academic researchers & experts	IRDiRC (various; consolidated feedback) OrphaNet (various; consolidated feedback)
Patient and Consumer Organisations	EURORDIS (various; consolidated feedback)

Based upon the feedback received, and numerous additional interactions with the above organisations, substantial revisions were made to each of the versions. The consultation time was extended.

D1. Survey launch and distribution

The finalised versions were each programmed into an online platform. They are accompanied by a home page, which explains who the intended audience for

that version is. In some cases, this includes a redirection to other versions when respondents could be expected to be part of more than one target group. A Privacy Notice prepared by the Commission was also made available, outlining how the data will be used and what steps will be taken regarding the confidentiality of the respondents.

The help of various international and European associations and networks was solicited to reach out to the targeted audiences at an organisational or national level. The coordinating organisations that were contacted, and the actions that they reported back as having undertaken to disseminate the information are summarised in Figure 42.

Figure 42 Information received on dissemination efforts of coordinating organisations

Version	Coordinating organisation (CO)	Actions taken by CO
1	EUnetHTA	Unknown
	Members of the EMA COMP	Unknown
	Members of the EMA PDCO and CAT	Unknown
	Members of the EC Pharmaceutical Committee (sent by DG SANTE)	Unknown
	European Social Insurance Platform	Unknown
	AIM Mutual	
2	EFPIA EuropaBIO	Forwarded the questionnaire to the joint EFPIA EuropaBio orphan medicine Task Force members
	EUCOPE	Unknown
	Plasma Protein Therapy Association	Unknown
3	Medicines for Europe	Sent survey out through internal mailing lists (several so called WGs- over 500 recipients)
4	OrphaNet	The call for the survey was published in the October 2018 edition of Orphanews.
	IRDIRC	The survey was included in IRDiRC's newsletter of October 2018. In addition, it has been published on IRDiRC's website in week 41 2018.
	European Reference Networks (ERNs)	Have contacted to EC with the request to be included in dissemination
5	EURORDIS	Disseminated the survey to 28 National Alliances and 62 European Federations (all in the EU / EEA)

In the course of dissemination of the survey to the initially identified coordinating organisations, several other organisations reached out with a request to participate. As this was considered of benefit to the reach of activities, these organisations were provided with the information needed to further disseminate the information. In addition, it was agreed that DG SANTE would contact the members of the Commission's pharmaceutical committee to cascade the survey information to Member States.

In the weeks following the launch of the surveys, various parties requested a copy of the survey that they could use to preview the questions and prepare their answers in an offline environment. The online platform itself does not

provide this functionality. Copies of the survey were subsequently sent to these parties, whilst emphasising those only online-completed responses could be included. By 26 October 2018, for each of the surveys a PDF version had been uploaded and linked to the home page of the survey.

D2. Response rate

Once the surveys were closed, upon collection of survey responses, all recorded responses which were considered test entries (not actual responses) were discarded from the analysis. The final response rate results are presented in Figure 43. A further breakdown of the respondents per target group is provided in the following Sections.

Figure 43 Final response rates on targeted surveys

Survey target group	# responses
National public authorities	42
Developers of orphan medicines and their representative organisations	43
Marketing authorisation holder of generic and biosimilar orphan medicines and their representative organisations	8
Academic researchers and experts	49
Patient and consumer organisations	13

D2.1. National public authorities

In total, 42 respondents submitted responses (some of which were incomplete). The largest category of respondents (19 respondents or 45.2%) are from national competent authorities or regulatory agencies, followed by national ministries of health (or similar) (8 respondents or 19%), national or regional health & social insurance organisations (5 respondents or 11.9%) and value assessment (HTA) organisations (3 respondents or 7.1%). One respondent currently works at other national health authority or agency, whereas 6 respondents indicated that they are employed in "other" type of organisations", such as international organisations.

The large majority of survey respondents (39 respondents or 95.1%) are based in EU Member States. In total, 19 EU Member States are represented individually in the survey, while 2 respondents provided answers on behalf of non-EU Member States, namely Iceland and Norway.

D2.2. Developers of orphan medicines

The survey for developers of orphan medicines was completed by 43 respondents, of whom 32 work for a pharmaceutical or biotechnology company with its own R&D activities. Other respondents work for national professional association for the pharmaceutical or biotechnology industry (n=4), for a European professional association for the pharmaceutical or biotechnology industry (n=3), for a pharmaceutical or biotechnology company without any own R&D activity (n=2), or at a not-for-profit scientific research organisation (n=2).

Among the 43 respondents, 24 (56%) work at an organisation with more than 500 employees (in full time equivalents). The second largest group (18.6% or

8 respondents) is employed by an organisation that has between 10 and 50 employees. The same number of respondents, namely 3, are currently working in an organisation that has between 251 and 500, and fewer than 10 employees; 2 survey participants represent an organisation that has between 51 and 250 number of staff. Such wide distribution allows to balance a high share of respondents from large organisations.

Out of 43 survey participants, 32 (74%) respondents work in an organisation that is not currently listed on the EMA SME Register. 31 respondents (72%) of the respondents' organisations is/has been a sponsor for an EU designated orphan medicinal product.

In total, 24 out of 38 respondents' organisations had obtained a marketing authorisation for one or more products, not limited to orphan medicines.

D2.3. Producers of generic medicines

This survey for producers of generic medicines was completed by 8 respondents, 7 of whom are representatives of companies with corporate headquarters in the EU/EEA region. Six out of 8 respondents represent companies that have more than 500 employees, the other 2 indicate that their organisations employ between 51 and 250 people.

D2.4. Academic researchers and experts

The survey for academic researchers and experts was completed by 49 respondents. Among survey participants, 41 (84%) are researchers in the field of rare diseases, 5 respondents (10%) work in the field of paediatric medicine and paediatric medicine development, 1 respondent (2%) is an expert in the field of orphan medicine development, and 2 survey participants are clinician and medical oncologists (4%).

The largest number of respondents was based in Italy (11 respondents or 23.4%) and Germany (8 respondents or 17%).

D2.5. Patient and consumer organisations

The survey for patient and consumer organisation was completed by 13 respondents, 7 of them are representatives of a European organisation for people living with rare diseases and/or their care givers, while 6 are representatives of a national organisation that has the same specialisation. Among 13 respondents, 5 did not represent a particular country, but rather work across Europe; 3 survey respondents indicated that their organisation is based in Ireland, while 1 respondent filled in the survey from Denmark, France, Germany, the Netherlands and Spain.

D3. Survey analysis

Survey responses to closed (multiple choice) questions were analysed quantitatively. Open questions, explanatory comments provided to closed questions and any supporting documentation provided were analysed qualitatively. In addition to having been incorporated into the analytical chapters of this report (Chapters 6 to 10), survey results have been presented more comprehensively in a separate synopsis report, accompanying this report.

Appendix E Online public consultation

Part of the study requirements for this evaluation was an Online Public Consultation (OPC). The online public consultation (OPC) was designed to collect opinions of people living with rare diseases and carers, as well as health care professionals (HCPs) who provide care to patients with such diseases (e.g. physicians, pharmacists). The survey was accessible between 12 October 2018 and 13 January 2019 via the online platform of the European Commission.

E1. Background and definitions

In the introduction to the online public consultation, background on the study was given alongside a definition of a rare or orphan disease and an orphan medicinal product: "A rare or orphan disease has been defined in the EU as a life-threatening or chronically debilitating disease that affects no more than five in 10,000 people. An orphan medicinal product means a medicinal product that is designated as such under the terms and conditions of the EU Orphan Regulation (No141 /2000). As a considerable number of paediatric diseases also qualify as a rare disease, the areas of orphan and paediatric medicines are closely linked."

The respondents were also provided with more information on the legal framework for orphan medicines and on the EU Orphan Regulation and an inventory of rare diseases. A full list of all orphan medicinal products was also provided.

E2. Response

The survey was completed by 145 individuals, of whom 105 self-identified as patients or individuals that have a direct personal experience with rare diseases and 40 identified themselves as HCPs. Among all respondents, 98 (68%) requested that personal details (name, organisation name and size, transparency register number) would be treated anonymously, while 47 respondents (32%) allowed to publish this information in a public domain. The here presented analysis provides aggregate results of responses only and is thus fully anonymous.

The majority of survey respondents (81, or 56% of respondents) identified themselves as EU citizens, with one individual response from a non-EU citizen. Although the OPC was in principle targeted at *individuals* and not at organisations²⁷³, responses were also received from representatives of non-governmental organisations (20, 14%), academic/research institutions (19, 13%), company/business organisations (8, 6%), public authorities (2, 1%) and an environmental organisation (1, 1%). One survey respondent indicated that he/she represents a national public authority and another respondent works in a regional public organisation. Of those responding on behalf of any

²⁷³ Organisational responses, such as those from patient advocacy organisations or public authorities, were sought out through a targeted consultation that was distributed via a number of umbrella organisations as explained elsewhere in this report. For completeness, we have nonetheless treated individual and organisational responses as equal and analysed the full set in this report.

organisation, the largest share of respondents indicate working for micro-sized (1-9 employees) or large organisations (≥ 250 employees).

The OPC survey was completed by individuals from 20 different countries. Some geographic clustering of responses was observed. The largest number of responses were received from Southern European countries - Spain (n=59,) and Italy (n=22). Whilst the number of contributors from Spain significantly stands out, review of their responses does not point towards a concerted campaign with alignment of answers.

According to the data collected, various responses were also received from Eritrea (5) and Martinique (3). However, additional information contained in these responses (organisation names and email addresses) suggest these actually originated from France and Luxembourg respectively. This signals that there may have been a technical error in the data collection system causing the country information to display incorrectly. Similar issues were not seen for responses from other countries.

Appendix F Economic analysis

The IQVIA-database containing information on medicine sales is an important data source for this study. Analyses of this database provided, amongst other things, input for the assessment of the economic value of the market reward and for the societal costs analysis. Chapters 7 (section 7.3) and 8 (sections 8.1 to 8.3) present the main results of these analyses. This appendix provides more detailed descriptions of the database and of the analyses carried out.

It contains the following parts:

- F1: Key characteristics of the IQVIA-database, including some limitations;
- F2: Preparation and use of the IQVIA-database;
- F3: Some methodological considerations with regard to the profitability and costs of the market rewards and incentives of the Regulation;²⁷⁴
- F4: Calculation of the economic value of the market exclusivity reward (article 8 of the EU Orphan Regulation);
- F5: Assessment of societal costs and health impacts.

F1. Key characteristics of the IQVIA-database (including some limitations)

For this study, the research team used (via third-party-access) the database '*Global Services- World Review Molecule*' of IQVIA (IQVIA MIDAS). IQVIA MIDAS (further to be called "IQVIA-database") integrates national audits of healthcare markets into a globally consistent view of the pharmaceutical market, virtually tracking products in hundreds of therapeutic classes and providing estimated product volumes and revenues through retail and non-retail channels.

The research team only had access to revenue and volume data for the period 2008 (first quarter) to 2017 (third quarter) for the geographical area '*Europe*'.

The following important characteristics and limitations of the dataset apply:

- As the scope of the dataset was limited to Europe, data for the US or Japan (for example) did not fall under the license, nor revenue and volume data for the years before 2008. Price data were not readily available, but have been derived from the revenue and volume data;
- For '*Europe*', and more specifically for the European Economic Area²⁷⁵, the dataset has some limitations. Firstly, data on the following five EEA-countries are missing in the dataset: Cyprus, Malta, Denmark, Iceland and Liechtenstein. Secondly, the dataset provides partial information (only 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;

²⁷⁴ This refers to work packages 4 and 5 of the tender specifications.

²⁷⁵ The EEA covers the 28 EU Member States, plus Iceland, Liechtenstein and Norway.

- Revenues in the IQVIA-database are based on list prices. In actuality realised prices may be different, for instance as a result of (usually confidential) price negotiations.
- The supply of orphan medicines may be underestimated given specific sampling issues applying for 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") not captured through nationally operating wholesalers.

The following table presents the list of specific variables available in the database.

Table 30: List of variables available in IQVIA-database

Variable	Short description	Variable	Short description
CTY_DESCR	CTY = Country	BIO_PRD	Biologic Products, Product contains a Biologic active ingredient (or a number of Biologics as active ingredients).
SEC	SEC = Sector	BIO_MOL	Biologic molecules identified by the usage of an IQVIA derived Biologics definition.
CRP	CRP Corporation =	ALL_BIOCOMP	AllBiocomp/Non-BiocompProducts, Biologic product segmentation based on regulatory approval pathway.
MNF	MNF Manufacturer =	BIOCOMP	Biocomparable Products, Detailed categorization for Biocomparable products.
ATC2, ATC2_DESCR, ATC3, ATC3_DESCR	ATC Anatomical Theory class =	NON_BIOCOMP	Non-Biocomparable Products, Detailed categorisation for Non-Biocomparable products.
INTPRD	International Product, Product name (international)	BIO_REF_GRP	Biosimilar Reference Product Group Links together biosimilar products with the reference product that is cited as part of the registration process.
INTPRD_CTY	International Product Country	PRD	Product name (local).
INTPRD_LDATE	International Product launch date	PRD_LDATE	(local) Product launch data.

Variable	Short description	Variable	Short description
MOL, MOL_LIST	Molecule (list), Active ingredient(s) based on International Non-Proprietary Names (INN)	GEN_PRD	Generic Products, market segmentation classification according to the IQVIA definition of original brands vs other products.
SALT	Chemical salt (Salt of compounds in products)	E_DT_PRTEXP	Estimated protection expiry date, estimated month and year of protection expiry date of a product.
NFC123, NFC123_DESCR	New Form code (for example, capsules, ampules)	PATEXP	Year and month of Patent expiry.
INTRX	International Prescription, Prescription Bound/Non Prescription Bound indicator status	USD_MNF_QTR_03_2008, EUR_MNF_QTR_03_2008 ²⁷⁶	Quarterly revenue data (available in USD, EUR, Local currency) ²⁷⁷ .
INTPCK	International Pack, Combination of international form, international size and international volume	UN_QTR_03_2008, SU_QTR_03_2008, KG_QTR_03_2008 ²⁷⁶	Quarterly volume data (available in units sold, in standard units sold, sales in terms of quantity of the compound consumed) ²⁷⁷ .

F2. Preparation and use of the IQVIA-database

For the analysis, information on the following three subsets of medicines was abstracted from the IQVIA-database:

- EU orphan medicinal products and their generics;
- Orphan-like products and their generics;
- Non-orphan products.

For each of these subsets the definition and method of identification is described below.

EU orphan medicinal products

²⁷⁶ These variables are only included as an example of the variables available quarterly.

²⁷⁷ In addition, yearly data is available for these variables.

The IQVIA-database does not provide an identifier for orphan medicinal products as such. Therefore, orphan medicines that received marketing authorisation in the EU were identified on the basis of the active substance present and the (local and international) product name (MOL and PRD and INTPRD respectively). More specifically, the following sub-steps were taken to come to the definition of the orphan medicines and the appropriate sales data (volumes, revenues):

1. A list of the orphan medicines with marketing authorisation in the EU was obtained from Orphanet Report Series (July 2018)²⁷⁸;
2. The list of tradenames obtained from sub-step 1 was matched to the list of product names in the IQVIA-database, on the basis of both product name (PRD) and international product name (INTPRD). The matching was conducted on the basis of:
 - the exact product name match;
 - the first word of the product name if the orphan medicine's tradename consisted of only one word; and of
 - the first two words if the orphan medicine's tradename consisted of only two words (Note, there are no products that have more than two words in their tradename).

This list was cross-checked with information provided to the study team by the EMA. The IQVIA-database does not include market data for all orphan medicines that received marketing authorisation in the EEA. In total EEA sales revenues until August 2018 were found for 105 orphan medicines that had not been 'prematurely' (i.e. before the end of the market exclusivity period) withdrawn from the EMA register;

3. For the identified matches, a list of active ingredients was extracted, based on International Non-Proprietary Names (MOL_LIST) together with the way the products are administered (NFC123);
4. All products with the same combination of (i) active ingredients and (ii) the way products are administered (combination of two variables: MOL_LIST and NFC123) were extracted from the database. It is further assumed that products that have the same combination of MOL_LIST and NFC123 as an identified orphan medicine (see step 2) are **generic products** for this orphan medicine.

Orphan-like products

As a second subset, a group of "orphan-like" medicinal products were identified. *Orphan-like* products are products that (i) acquired an orphan designation in the US before the year 2000 and were marketed in the US, and (ii) at the same time were marketed in the EU but did not receive an orphan designation in the EU. The EU Orphan Regulation entered into force in 2000; therefore prior to 2000 manufacturers could only obtain an orphan designation and marketing authorisation in the US. It is assumed that these

²⁷⁸ Available at https://www.orpha.net/orphacom/cahiers/docs/GB/list_of_orphan_drugs_in_europe.pdf, last accessed in August 2018.

orphan-like medicinal products have 'orphan' characteristics, such as (potentially) low sales volume and use in the treatment of somewhat rare diseases²⁷⁹.

The identification of the group of *orphan-like* products offers a possibility for comparison with the orphan medicines in the EU. The steps followed to identify these products in the IQVIA-database are similar to the sub-steps described above for orphan medicines:

1. A list of US orphan medicinal products was obtained from the website of the FDA²⁸⁰;
2. A list of tradenames obtained from sub-step 1 was matched to the list of product names in the IQVIA-database (on the basis of international product names). The matching was conducted on the basis of the exact product name match, of the first word of the product name if the tradename consists of only one word, and of the first two words if the tradename consists of only two words and so on, depending on the number of words in the tradename of a US orphan medicinal product. All identified products are assumed to be *orphan-like* products;
3. Those products that were present in the EU market as an orphan medicine were removed from the list of matched products resulting from the previous sub-step. These products were identified on the basis of active ingredients and the way the medicine is administered (MOL_LIST and NFC123);
4. For the remaining group of products, a list of active ingredients based on International Non-Proprietary Names (MOL_LIST) together with the way the products are administered (NFC123) was extracted;
5. All products that have the same combination of active ingredients and the way products are administered (combination of two variables: MOL_LIST and NFC123) were extracted from the database. It is assumed that products that have the same combination of MOL_LIST and NFC123 as an identified *orphan-like* product (see step 2) are **generic products** for this *orphan-like* product. A number of orphan-like products have the same list of active ingredients and the way the medicine is administered, therefore the generics that are identified could be a generic product for all of those branded products.

Sub-steps 2 for the EU orphan medicines and US *orphan-like* medicinal products (and their generics) have several limitations. First, branded products were identified on the basis of a trade name, but potentially products might be marketed under different trade names in different countries. It is therefore

²⁷⁹ Under the US Orphan Drug Act a rare disease was defined as one that affects fewer than 200,000 people in the US (approx. 7 in 10,000). This is slightly different from the definition under the EU Orphan Regulation. See also Chapter 2 of the main report.

²⁸⁰ The following search criteria were used: (i) Specific search criteria for the website: all dates, search results 'All designations', output format 'Download Excel file' (ii) Selection criteria within the extracted file: Marketing approval date before 2000.

Source is <https://www.accessdata.fda.gov/scripts/opdlisting/oopd/>.

possible that for such products, the volumes of branded products have been understated.

Furthermore, sub-steps 4 for EU orphan medicines and 5 for US *orphan-like* medicinal products may have resulted in capturing more generic products than there are on the market for these specific branded products. For example, in case of Pedea, identification of generic products on the basis of the molecules list and the way it is administered, included products that are used for purposes other than the orphan indication. Here, the existence of generic entry may thus be overstated when the use of the identified generics is different from the specific use of the orphan medicine.

Non-orphan medicines

In various analyses the findings for orphan medicines or orphan-likes have been compared with those of non-orphan medicines. This has been done, for example, to compare the level of annual sales, competition from generics and the economic value of market exclusivity.

Therefore, *non-orphan medicines* were identified separately in the IQVIA-database, using the following steps:

- Orphan medicinal products and *orphan-like* products were filtered from the IQVIA-data by matching the complete list of IQVIA data with previously made lists (of orphan medicines and orphan-like products) on the basis of international product names. Products with a 'one worded' international product name were matched on one word, products with a 'two-worded' international product name were matched on two words, etc. Subsequently, the matched products were filtered from the IQVIA data. The remaining list was regarded as containing only non-orphan medicines;
- Depending on the type of analysis carried out, subsequent selections were made from this group of non-orphan medicines:
 - For the analysis regarding time to EEA market and spread within EU12 market, a group of non-orphan medicines with an international product launch date after 1995 was used;
 - For the analysis regarding average annual sales revenues in the EEA, a group of non-orphan medicines that contained new molecules (based on the international product launch date) and were launched in the EEA after 1999 was selected. The quarterly sales revenues per unique international product name were summed across all countries. Consecutively, all products with a quarterly sales revenue of zero in all EEA/EU countries were removed from the dataset;
 - For the analysis regarding the economic value of patent protection, only the group of non-orphan medicines with a patent expiry date (a variable in the database) between 1 January 2011 and 1 January 2015 was selected. This selection enabled analysis of non-orphan medicines with sales revenues for at least three years before expiration of the patent, as well as at minimum two years after expiration of the patent.

Selection of 16 orphan medicines for the analysis of the market exclusivity reward

To assess the economic value of the market exclusivity reward (see Section F4 in this Appendix), a group of 16 orphan medicines was selected for further analysis. This group was selected based on the following two criteria: (i) the market exclusivity period ended and (ii) there is at least two years of data available in IQVIA-database after the end of the exclusivity period. These criteria are used as it is assumed that a potential generic product would enter a market within two years after market exclusivity expires. Based on these selection criteria the following orphan medicines were selected (Table 31).

Table 31 Orphan medicines included in analysis of the market exclusivity reward

Tradename	Active substance	MA Date	ME Expiry
ALDURAZYME	Laronidase	12-6-2003	12-6-2013
BUSILVEX	Busulfan	11-7-2003	11-7-2013
CARBAGLU	carglumic acid	28-1-2003	28-1-2013
FABRAZYME	agalsidase beta	7-8-2001	7-8-2011
GLIVEC	imatinib mesilate	12-11-2001 ^(a)	12-11-2011 ^(a)
LITAK	Cladribine	19-4-2004	19-4-2014
LYSODREN	Mitotane	30-4-2004	30-4-2014
ORFADIN	Nitisinone	24-2-2005	24-2-2015
PEDEA	Ibuprofen	2-8-2004	2-8-2014
PRIALT	Ziconotide	24-2-2005	24-2-2015
REPLAGAL	agalsidase alfa	7-8-2001	7-8-2011
SOMAVERT	Pegvisomant	15-11-2002	15-11-2012
TRISENOX	arsenic trioxide	7-3-2002	7-3-2012
VENTAVIS	Iloprost	18-9-2003	18-9-2013
WILZIN	zinc acetate dihydrate	18-10-2004	18-10-2014
ZAVESCA	Miglustat	21-11-2002	21-11-2012

Note: MA = marketing authorisation date, ME = market exclusivity expiration date. (a) Glivec has multiple orphan designation, from which only one date was included in this table.

For these selected 16 orphan medicines, an additional cleaning step was conducted. The IQVIA-database was manually checked to identify branded and generic products. The check was conducted on the basis of when a product was launched (product launch date), the manufacturer, and the way the product is administered²⁸¹. In the case of 'Pedeas', the IQVIA-database identifies over 6,000 matches resulting from the four sub-steps set to identify

²⁸¹ Specifically for this step the website of EMA was consulted together with EPAR summaries for the public for the 16 selected orphan medicines (see for example, https://www.ema.europa.eu/documents/overview/aldurazyme-epar-summary-public_en.pdf and <https://www.ema.europa.eu/medicines/human/EPAR/aldurazyme>, last accessed in September 2018).

the EU orphan medicinal products (see above). Given the large number of products and extensive usage of its active substance (ibuprofen), only the branded infusion product was considered for further analysis.

Calculation of data for the groups of medicines

For the sub-sets of products described above, various calculations were performed, such as total revenues, sold volumes and the price. Total revenues for the sales of a product were calculated as a summation of available sales data (in euro) for each quarter between the first quarter of 2008 and the third quarter of 2017.

Total sold volumes were calculated as a sum of volumes for each product. Specifically, volumes were measured in standard units²⁸². This measure, however, has a limitation that dissimilar items are not normalised to an equivalent volume.

Price was calculated as total revenues divided by total sold volumes measured in standard units; this gives a value in euro per standard unit. Some orphan medicines are administered through either injections or capsules. For these orphan medicines, a "most sold type" (injection or capsule) was determined to calculate the price.

The calculation of the economic value of the market exclusivity reward was based on (i) the actual development of the revenues of the originator company, (ii) the applicable comparator situation and (iii) the market dynamics after the expiry of the exclusivity rights. Section F4 provides further details.

To determine availability, i.e. how fast orphan medicines and orphan-likes enter the EU/EEA market and in how many countries they become available, a number of assumptions were made:

- The launch dates in the IQVIA-database are reported as a combination of a month and year that a product was launched. Therefore, time to reach the EU/EEA market is calculated in months;
- If an identified orphan medicine is available on the market before the marketing authorisation date (e.g. through compassionate use programmes), this product is assumed to become available as an orphan medicine at the moment of marketing authorisation. Specifically, local product launch date (PRD_LDATE) was used to determine this for the EU orphan medicines and international product launch date (INTPRD_LDATE) for orphan-likes. For orphan-like products, it is additionally assumed that an internationally launched product becomes instantaneously available on the US market if it was launched outside of the US;

²⁸² Standard units are defined by IQVIA as the number of standard 'dose' units sold. It is determined by taking the number of counting units sold divided by the standard unit factor, which is the smallest common dose of a product form as defined by IQVIA. Counting units are the number of tablets, millilitres of liquid, grams of ointment sold. It is determined by multiplying the number of packs sold (units) by the size of the pack in tables, capsules, millilitres, etc. Source: IQVIA MIDAS Data Attributes, Measures and Statistics (2018), last accessed in September 2018.

- If products that have been associated with a specific orphan medicine or orphan-like product, but that appear in the dataset under different names, are recorded as having entered an EU/EEA country on different dates, it is assumed that the product becomes available in that country at the earliest date. For example, if the data set contained two separate entries for 'FABRAZYME' and 'FABRAZYME >>>', which both appear to refer to the same orphan medicine (namely 'Fabrazyme'), and one entry indicates the product became available in Germany in January 2000 and the other in March 2003, it is assumed that product entered the German market in January 2000.²⁸³
- For a number of products, the product launch date (either international or local) was not available in the dataset. These products are thus not taken into account in further calculations of how fast the product becomes available on the EU/EEA market. They are, however, included to calculate the number of countries the product reaches within EU/EEA;
- If an orphan medicine or orphan-like medicine has more than one marketing authorisation date (due to it being authorised for more than one indication), the time difference between when a product enters the EU/EEA market and the marketing authorisation date is calculated using the first marketing authorisation date. This assumption is made because within the IQVIA-database it is not possible to determine for which indication the product is available on the market.

Analyses carried out involving groups of products

Various analyses were carried out involving one, two or three of the identified sub-sets of products. Apart from the analysis to assess the economic value of the market exclusivity reward, this concerns the following:

Analysis of level of turnover

For orphan medicinal products, orphan-likes and non-orphan medicines an assessment was made of the turnover realised. For the group of non-orphan medicines the analysis specifically focussed on recently introduced products, i.e. products which were not visible in previous years in the database. This selection was made to have a group with characteristics (new introduction) that are comparable to those of the other groups. The results from the analysis have been presented in Chapter 6 of the main report.

Level of generic competition and economic value of market exclusivity / patent protection for non-orphan medicines

Similar to the analysis of the economic value of the market exclusivity reward as explained in Section F.4, an analysis was carried out on the level of competition for non-orphan medicines. Here, competition can emerge once a patent and, if applicable, SPC has expired. If this happens, a price drop of the branded product may occur, and a new equilibrium price may be established. The results of this analysis are presented in Section F. 4 and in Section 8.2 of the main report.

²⁸³ The names of the product and dates are used only as an example and do not come from IQVIA MIDAS database.

Entry of generic competition in relation to US patents

Further to the analysis of the scope and impact of generic entry for orphan medicinal products, it was analysed to what extent a patent or SPC protection in the US has impact on the emergence of generic competition in the EU. To this end, for the group of orphan-like products the product launch dates of generics in the EU market has been compared to the date at which a patent or SPC of a branded product expires in the US. The results for this analysis have been presented in section 8.3 of the main report.

Analysis of average lead time between marketing authorisation and first entry in the EU market

For orphan medicines and orphan-like products the time period between marketing authorisation and product launch in the EU was analysed. A similar analysis has been carried out for non-orphan medicines, but in this case the analysis was based on the difference between international product launch date and product launch date in the first EU country. The results for these analyses are presented in section 7.3 of the main report.

Analysis of spread of medicines within EU

For orphan medicines and orphan-like products, it was analysed in how many Member States sales of the product were recorded three years after the initial marketing authorisation date.

For non-orphan medicines, a similar analysis was carried out, but in this case based on the date three years after the international product launch date. The results for these analyses are presented in section 7.3 of the main report.

For orphan medicines it was further analysed in how many Member States sales of a product were visible in the period 2008-2016. This analysis is presented in section 5.8 of the main report.

F3. Some methodological considerations

Results from the analyses of the IQVIA-database are the main input for the analysis presented in Chapter 8 on the relation between costs and benefits to different groups of stakeholders. Alongside the analysis further described in Section F5, this assessment also calls for an estimation of the economic value of the market exclusivity reward.

The basis for this analysis is the assumption that the EU Orphan Regulation provides a way to overcome market failure for orphan medicines, resulting from relatively small markets for orphan medicines and limited potential to recover development costs through product sales. The market exclusivity reward was introduced as an incentive to product developers, as it offers the possibility to be shielded from competition during this period: the developer can potentially cater for the whole EU market during this period.

After this period of market exclusivity (and the end of the patent/SPC protection and other regulatory protections), competition ('generic entry') is allowed. Generic entry will occur when the production costs of the orphan medicine (including starting up the production line) are sufficiently below the expected sales revenues, and when the market is deemed to be sufficiently large to be catered for by more than one supplier. As such, the market entry

of generics shows that a more or less competitive market exists after the end of the market exclusivity and patent period.

If generics do not enter the market after expiry of protections, it may well be concluded that a product would also not have been developed and brought to market in the situation without the Regulation. The reason for this assumption is that, at this stage, when an originator has already developed the product, the costs for entering the market are substantially lower than in the previous stage and the barrier to market entry is substantially lower. As such, the absence of generic entry provides an indication that the Regulation may have stimulated the development of the orphan medicine. The opposite is not necessarily true, however. The entry of generics into the market can signal two different situations:

(1) Without the EU Orphan Regulation, the orphan medicine, as well as – at a later stage – the generic version would still have been developed. Therefore, here the comparator situation is that the Regulation has had no appreciable effect (and consequently has offered compensation to the sponsor of the orphan medicine sponsor that was not needed to correct market failure);

(2) Without the EU Orphan Regulation (and market exclusivity incentive for the sponsor of the orphan medicine), generics would not have been developed due to the R&D costs and risks involved. Assuming that the cost/risk situation was the same for the orphan medicine developer, it may be concluded that in these cases the EU Orphan Regulation has been effective in stimulating the development of the orphan medicine.

In cases where the comparator situation would have been “*no orphan medicine available*”, the question still remains whether or not the market exclusivity reward has resulted in overcompensation. This could be the case if the extra sales revenues brought about by the market exclusivity period in the EU market are substantially higher than the attributable²⁸⁴ R&D costs for the orphan medicine.

The existence of overcompensation can be assessed in two ways:

(1) In the case of generic entry, the price of the orphan medicine may decrease after the period of market exclusivity. The size of the decrease may signal the extra mark-up applied during the market exclusivity period for the orphan medicine. This extra mark-up realised in the sales over the 10 year market exclusivity period can subsequently be compared to the average R&D costs of an orphan medicine;

(2) In case there is no generic entry, the price of the orphan medicine may not change (substantially) after the period of market exclusivity. In this situation, it is difficult to assess whether or not there is overcompensation.

For both situations, the dynamics of generic entry are important. Three approaches were used to get a better understanding of whether or not generic entry has taken place in the EU or could reasonably be expected.

First, the research team carried out a detailed analysis of a specific sample of orphan medicines in the EU market. Of the 107 orphan medicines available

²⁸⁴ It has to be taken into account that also on other markets extra revenues may be generated which cover part of the R&D costs.

in the EU in 2017-Q3 and for which market data was available²⁸⁵, 16 orphan medicines were in a situation where (1) the market exclusivity had expired and (2) two years of market data²⁸⁶ after expiry were available (effectively since Q4 2015 or earlier). The information on the market exclusivity period was further combined with MPA information²⁸⁷ on the patent/SPC status of these orphan medicines. This approach and the results of the analysis are presented in Section F4 of this Appendix.

Due to still existing protection layers and lack of generic entry, from this group of 16 orphan medicines only four orphan medicines could be used to calculate the economic value of the market exclusivity. Although the analysis gives a complete picture, in that the economic value has been assessed for all orphan medicines that have seen competition from generics for at least two years, the basis for drawing conclusions is relatively small. Therefore, two additional analyses were carried out.

The first concerns an assessment of the pricing of products with similar characteristics as orphan medicines (orphan-likes), in relation to generic entry. The underlying idea is that the existence of generic competition for these orphan-like products in the EU market could give an indication of the 'normal' level of price competition to be expected for orphan products.

The second concerns the pricing of other branded products in relation to generic entry (the non-orphan medicines). Here, the pricing of a sub-set of newly developed non-orphan products was analysed in relation to market entry of generics. In this analysis a similar approach was followed as for the orphan medicines. However, as the non-orphan medicines do not receive market exclusivity, the compensation is based on the prices of branded and generic products after the end of the protection offered by a patent or SPC.

F4. Calculation of the economic value of the market exclusivity reward

As part of this study the economic value of the market exclusivity reward was estimated. For this analysis two dimensions are important: (i) the monetary impact of the reward for society as a whole and (ii) the actual comparator situation. Both of these dimensions are briefly discussed here.

Monetary impact of the reward for society as a whole

As described, the market exclusivity reward creates an additional protection layer against the 'regular' forces of competition that pharmaceutical companies face.²⁸⁸ This additional protection layer may (but not necessarily

²⁸⁵ The IQVIA-dataset does not include market data for all orphan medicines; in total, we found EU sales revenues for 107 orphan medicines.

²⁸⁶ This period of (at least) two years was chosen to ensure that any appearing generic competition could be observed and that there is sufficient time for the market to reach a new equilibrium.

²⁸⁷ MPA Business Services Limited (MPA), see: <http://mpasearch.co.uk/aboutus>.

²⁸⁸ Given the use of temporary exclusivity rights like data exclusivity and market protection, the dynamics of competition deviates already from other less regulated markets.

does²⁸⁹) result in a longer period of non-competitive pricing, as the market entry of competing lower priced generic medicines is not (yet) allowed. As a result of this longer period of market protection and delayed generic entry, society is unable to benefit from increased competition and lower prices for the used medicines. In economic literature this relates to the so-called 'deadweight loss'.

The market outcome will be influenced by a number of determinants, for example:

- the price setting of the originator product over time: in some cases producers lower their prices already in anticipation of future competition to stimulate brand loyalty, while in other cases the prices are kept at a maximum in response to national pricing rules.
- the creation of competitive pressure by a generic competitor (fast time-to market? Price pressure?)
- substitution effects: do patients (or prescribing physicians) change their actual usage from the originator to the generic product?²⁹⁰

In the 2009 Sector Inquiry, DG Competition assessed the potential (societal) cost reductions that could have been realised for regular pharmaceutical products, if competition would have resulted in the market entry of generic pharmaceutical products immediately after the end of market exclusivity.²⁹¹

The comparator situation

The principal comparator situation used in this study is the situation without the EU Orphan Regulation, i.e. the situation before the EU Orphan Regulation came into force and in which no specific market exclusivity reward in the EEA was available. However, this comparator situation is not always easy to define, as various factors play a role.

First of all, *multiple protection layers* may apply which to some extent may overlap in time and contribute to the same effect as that of market exclusivity, namely delay of generic entry. A 2018 study by Copenhagen Economics²⁹² on supplementary protection certificates illustrated this for a number of designated orphan medicines. For instance, the case of Tobi

²⁸⁹ Due to the (potential) overlap over various protection levels, it is possible that (for example) the protection through a SPC-extension exceeds the 10-year market exclusivity.

²⁹⁰ Technopolis & Ecorys (2016), 'Study on the economic impact of the Paediatric Regulation, including its rewards and incentives'.

²⁹¹ European Commission, DG COMP (2009), Sector inquiry of the pharmaceutical market', final report, consideration 216-217. Within the sample of studied medicines, the average time-to-market was seven months; for the most selling medicines, the average time-to-market was about four months. The sector inquiry concludes: "In relation to a sample of medicines analysed, the report estimates that savings due to generic entry could have been 20% higher than they actually were, if entry had taken place immediately following loss of exclusivity. According to the analysis the expenditure amounting to about € 50 billion would have been about € 15 billion higher without generic entry. However, additional savings of some € 3 billion could have been attained, had entry taken place immediately." (op cit., p 521)

²⁹² Copenhagen Economics (2018), 'Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe', p. 321 and further.

Podhaler® shows that, while the patent protection will end in 2021, the protection through a SPC (until 2026) exceeds the 12-year market exclusivity (until 2023, including a two-year paediatric extension).²⁹³ This complicates the calculation of the economic value of the orphan market exclusivity reward, as the combined (and extended) protection levels vary in their scope and are difficult to disentangle. This difficult disentanglement also applies for the case of Revlimid®, where three overlapping periods of market exclusivity were granted (for different orphan indications).

A second factor in the comparator situation is the impact of *similar regulatory systems* outside the EU, most notably the US (where the Orphan Drug Act was introduced in 1983). If the incentives of the US system already ‘trigger’ the development and marketing of medicines for rare diseases, which can also be used on the EU market, it can be argued that the actual effectiveness and value added of the EU Orphan Regulation would be zero. However, again this effect is difficult to disentangle because investors may base their investment decision on the expectation that in both jurisdictions an exclusive right like the market exclusivity will be received.

Thirdly, there are also situations where the pharmaceutical product was initially developed and obtained marketing authorisation as a regular (non-orphan) pharmaceutical product, and its development and subsequent authorisation as a designated orphan medicine follows later. In such cases as well the impact of the EU Orphan Regulation is difficult to disentangle from other incentives and factors influencing the investment decision. Related to the previous situation, is the situation where the original compound was developed before the introduction of the EU Orphan Regulation (or the US Regulation), but now also is used for the treatment of an indication which falls under the EU Orphan Regulation. A specific example is Ibuprofen, for which the original patent was filed in 1962, but a new formulation was granted orphan designation and received market exclusivity upon its marketing authorisation in 2004 (the orphan medicine Pedeia, for the treatment of ‘patent ductus arteriosus’ in preterm new-born infants).

Assessing the economic value of market exclusivity

To assess the economic value of market exclusivity, several steps were taken.

Cleaning and preparation of the dataset - Third-party-access was gained to the dataset ‘Global Services- World Review Molecule’ of IQVIA, which contains detailed data on (orphan) pharmaceutical products, including information on the manufacturer, molecules, the product (name, international launch date, etc.), sales indicators (including sales data), and volume indicators (including sales data). See Section F1 for details on the cleaning and preparation of this dataset.

Selection of 16 orphan medicines – As indicated, a group of 16 orphan medicines was selected for further analysis. This group is characterised by the fact that (i) the market exclusivity period has ended and that (ii) there is at least two years of sales data available in the IQVIA-database after the end of the exclusivity period. The second selection criterion made it possible to

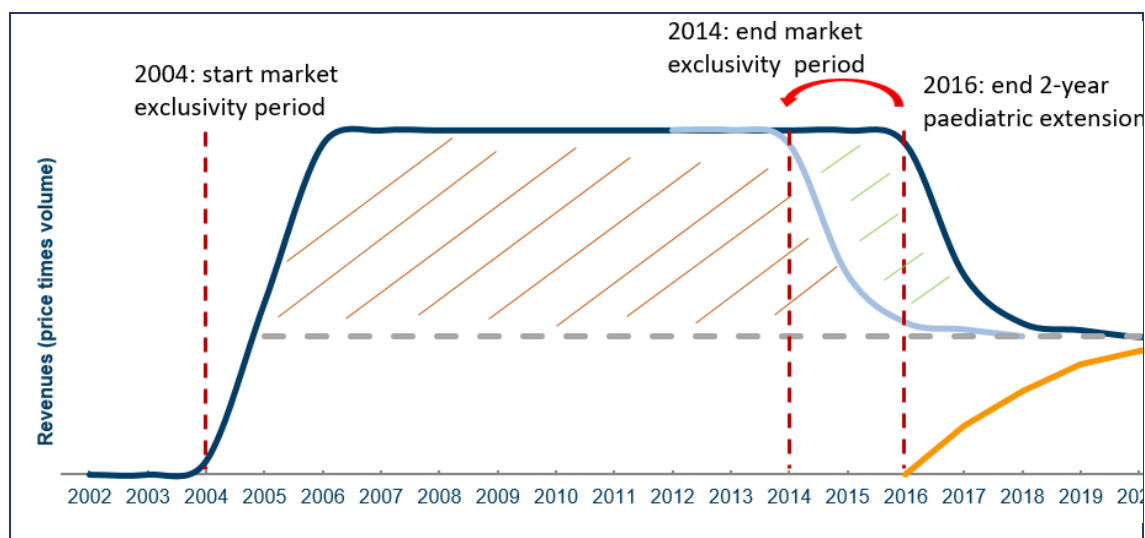
²⁹³ In this specific case a ‘superior’ rival product (Vantobra) entered the market in 2015, so before the end of the market exclusivity period.

observe the dynamics in the market. This period of (at least) two years was chosen to ensure that any generic competition could be observed and that there was sufficient time for the market to reach a new equilibrium. To strengthen the understanding of the comparator situation, the IQVIA-database for these 16 orphan medicines was enriched with the data from MPA on applicable protection layers (patents, SPCs).

Approach calculation of the economic value – The calculation of the economic value of the reward is based on (i) the actual development of the revenues of the originator company, (ii) the applicable comparator situation and (iii) the market dynamics after the expiry of the exclusivity rights.

Figure 44 illustrates how the economic value of the reward can be calculated. Various elements are relevant here. First, the dark blue line represents the actual development in revenue over the period 2004-2016, after which the protection ends and generic entry may occur (orange line). Second, the paediatric extension to the orphan market exclusivity delays the generic entry with two years. Without this protection, the decrease in revenue would likely have occurred two years earlier (light blue line). Third, once the protection ends, the market reaches a new equilibrium (grey line). The size of the economic value of the orphan market exclusivity is represented by the striped areas, as the market equilibrium could (in theory) have started in 2004. A distinction can be made between the 10-year market exclusivity period (striped orange area) and the additional 2-year paediatric extension (striped green area).

Figure 44 Illustration calculation economic value



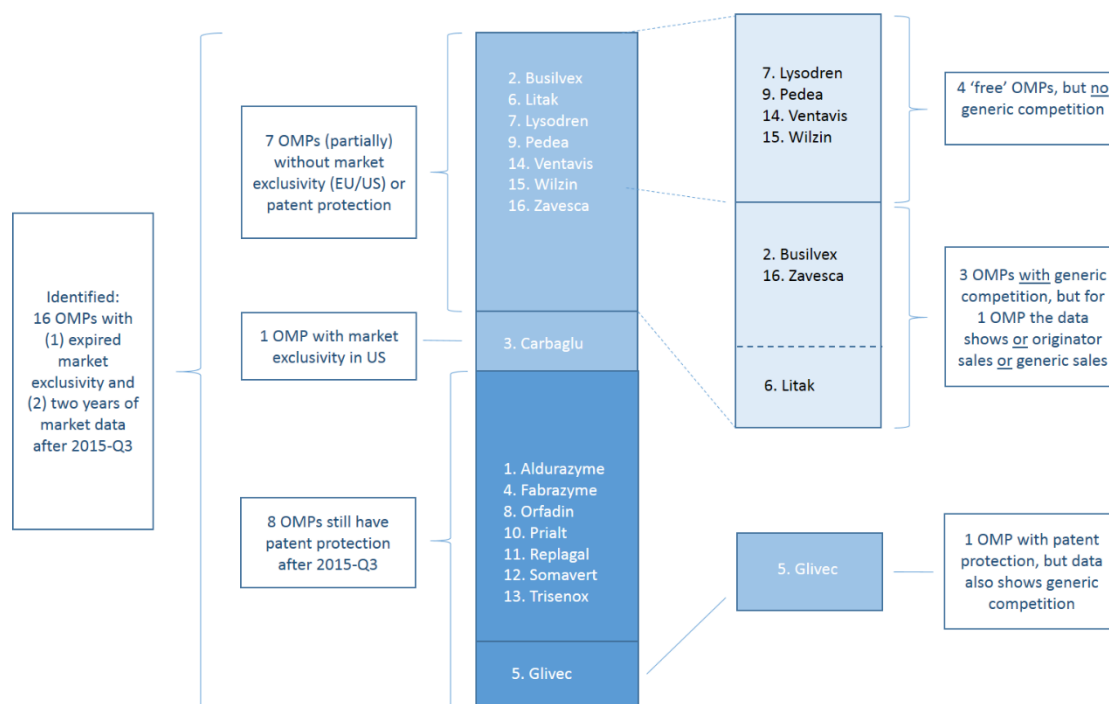
Note: high-level assumptions are: (i) after the marketing authorisation in 2004, the revenues of the originator increase and stabilise; (ii) after the end of the 2-year paediatric extension, a generic entrant gains market share and the market reaches a new equilibrium; (iii) without the 2-year paediatric extension, the decline in revenue of the originator would have started two years earlier. Please note that IQVIA-data is available for the period 2008 – 2017 (third quarter).

Based on the IQVIA-database and other external sources (like EMA reports), key economic indicators like the entry of a generic competitor, the actual development of the revenues of both the originator company and generic company were assessed. As a threshold, the new generic price was used only if there were at least two quarters of market data.

The comparator situation & results of the calculation

As explained above, there are various factors that influence the comparator situation, especially the existence of other protection layers and the rise of generic competition. In the next figure, these key elements have been summarised for all 16 orphan medicines that were selected for further analysis. Subsequently, these elements are further explained.

Figure 45 Summary protection layers and generic entry for 16 orphan medicines



- As described, the 16 orphan medicines were selected which fulfilled the criteria of market exclusivity period and availability of sales data;
- The additional MPA-data on applicable protection layers (patents, SPCs) showed that for eight of these orphan medicines there still existed patent or SPC protection after 2015-Q3 (applicable for Aldurazyme, Fabrazyme, Glivec, Orfadin, Prial, Replagal, Somavert and Trisenox). Within this group, generic competition was observed for Glivec in 2017; the patent/SPC protection ended in December 2016. In addition, it was observed that one orphan medicine (Carbaglu) was still under protection from market exclusivity offered under the US Orphan Drug Act (the US market exclusivity ended in March 2017); generic entry was not visible for this product on the EU market in the period up to 2017-Q3;
- The remaining seven orphan medicines are without any 'protection' after 2015-Q3, although Zavesca received a second market exclusivity reward on a separate orphan indication (for the period 2009-2019). For four orphan medicines (Lysodren, Pede, Ventavis, and Wilzin), no generic entry was observed. This lack of generic competition may be related to the relatively low annual sales volumes during the period 2008-2015-Q3. For three orphan medicines (Busilvex, Litak, Zavesca) generic competition was observed after expiry of the market exclusivity;
- Given these specificities, it was possible to calculate the economic value of the market exclusivity reward for four of the 16 orphan medicines. The estimation results in a value ranging from €2.4m to €5.1b. This represents 12 to 54% of total revenues for the individual products during this period, the average for these four being 30%. In other words, the average

economic value of the market protection for these four products amounts to 30% of revenues.

It is noted that for each of these four products multiple protection layers exist(ed). This implies that the estimated economic value of the protection cannot be linked only to the market exclusivity reward, but also to other protection layers.

The role of US patent protection in the emergence of competition

As described, in one of the 16 cases in which market exclusivity had ended, there was no generic entry visible in the EU in the following two years; at the same time the product still had a patent/SPC in the US. This observation gave rise to the question to what extent protections in the US impact the emergence of generics in the EU. To assess this, information on the group of orphan-like products was used to analyse the extent to which entry of generic products could be seen in the EU before the expiration of protections in the US.

National product launch dates in the EU were compared to the end date of the patent/SPC in the US, as published by the FDA. For 52 out of the 84 orphan-like generic entry was indeed observed in the EU. In 47 of these 52 cases (90%), the first national product launch date in an EU Member State falls before the end date of the US patent/SPC of the product. It thus seems that the existence of a US patent/SPC does not necessarily hinder the entry of generic products in the EU.

Assessment of the market value of patent protection of non-orphan medicines

Similar to the analysis described above, it was analysed to what extent the economic value can be calculated for protection, in this case patent/SPC protection, of non-orphan medicines. This analysis helps to assess the calculated economic value of market exclusivity for orphan medicines, as non-orphan medicines have a similar possibility of patent/SPC protection as orphan medicines do, but cannot receive the additional protection offered by market exclusivity. It can thus act as a control group.

Further to the steps described before for the construction of the group of non-orphan medicines, the following steps were taken:

1. A selection of products was made with a patent/SPC expiry date between 01-01-2011 and 09-01-2015
This selection was made such that years of revenue of generics and branded products before the patent/SPC expiry as well as after the patent/SPC expiry date were observed.
2. The price of branded products and generic products was calculated per quarter
First, the revenues and the standard units sold of all generic products and all branded products (sometimes there are several branded products with different manufacturers) were summed. Second, the average price of branded and generic products was calculated by dividing revenues by the volume of standard units that were sold within a quarter.

3. The equilibrium price was calculated per market and per quarter
The assumption was made that the equilibrium price of a market (market is a combination of ID product and country) equals the average price of generic products in the third quarter of 2017 (last date point for which revenues and standard units sold are available).
4. The counterfactual revenues for branded and generic products were calculated
The counterfactual revenues are the revenues that would be realised in the market if the standard units had been sold at the equilibrium price. The counterfactual revenues are therefore calculated by multiplying the standard units per market for generic and branded products with the equilibrium price.
5. The economic value of the patent is calculated per quarter and per market for branded and generic products
The economic value is calculated by subtracting the counterfactual revenues per market from the actual revenues.
6. The relative value of the patent is calculated for branded and generic products
The economic value of the patent is calculated as a percentage of the revenues.

This analysis comprised 342 products that are marketed in the EEA. In 105 out of these 342 cases generic entry was observed (31%). The products with generic entry account for 55% of total revenues for this group, implying that average revenues for such products are higher than revenues for products without competition. The average premium for the 105 products with competition was 41%.

The results are not completely comparable to those for orphan medicines. A main difference is that the period of competition from generics may be longer than the period taken into account for the orphan medicines, as patents/SPCs may have expired already in 2011-2014. Nevertheless, the level of competition for non-orphan medicines (31%) seems to be somewhat less than that for orphan medicines (4 out of 9, or 44%).²⁹⁴ Also, in the case of non-orphan medicines, competition not always emerges in the years immediately following expiry of a patent.

Moreover, it appears that the level of economic value of patent/SPC protection for non-orphan medicines (thus without market exclusivity) is in the same range as the economic value of protections including the market exclusivity calculated for orphan medicines (i.e. 41%, as compared to on average 30% in the case of orphan medicines). The tentative conclusion from this comparison is that the level of protection provided by the EU Orphan Regulation is such that the situation for orphan medicines is not considerably different from that for non-orphan medicines.

²⁹⁴ In this comparison Glivec was included even though its patent/SPC protection had ended less than two years before the end of 2017-Q3. If Glivec is excluded, the comparable level of generic entry for orphan medicines is three out of eight (38%).

F5. Assessment of societal costs and health impacts

This section provides the details of the analysis of societal costs and health impacts of the EU Orphan Regulation, as described in chapter 8 of the main report. The analysis follows the methodology of a cost-benefit analysis (CBA), but is different from a CBA in that the health benefits are not expressed in monetary values, but in terms of quality adjusted life years. As such, the analysis is similar to a cost-utility analysis (CUA) as carried out at the level of individual orphan medicines in HTA reports.

F5.1 General observations on the analysis

This analysis is based on the information gathered and the results of the analyses carried out in this study regarding the effectiveness of the EU Orphan Regulation. Societal costs and health impacts were assessed by comparing the “situation with the EU Orphan Regulation” to the most likely (though hypothetical) historic “situation without the EU Regulation” (comparator situation).

The analysis is essentially backward looking; costs and health impacts relate to the years 2000 up to and including 2017. This implies that any costs or health impacts generated by the EU Orphan Regulation in 2018 and beyond are not taken into account. As the use of orphan medicines continued after 2018, this implies that also costs and health impacts continued to occur. Where relevant the impact of the restriction to the period 2000-2017 is highlighted.

Costs for these years 2000-2017 were, as far as possible, calculated at a 2018 price level. In case costs or benefit items relate to previous years, prices were adjusted to the 2018 level by using the Eurostat harmonised index of consumer prices for the EU.

Furthermore, all costs were discounted to the **base year 2018** using a discount rate of 3%. This way of discounting implies that costs incurred in previous years are valued higher than costs incurred in 2018. For instance, when using a discount rate of 3%, the discounted value in 2018 of costs incurred in 2017 is 103% of the nominal value of the costs made in 2017 (expressed in 2018 prices); for costs incurred in 2016 the discounted value is $1,03^2=1,0609$ times the nominal value incurred in 2016 (expressed in 2018 prices).²⁹⁵

The 3% discount rate is used as it is the prescribed societal discount rate for investment projects financed by the EU in non-cohesion countries²⁹⁶. It is

²⁹⁵ The application of discounting implies that there is a difference between the discounted value (present value) of costs and benefits and their nominal value. The nominal value represents the sum of the values that occur in each of the years 2000-2017. The discounted value 2018 means that costs or benefits that occurred in the distant past are valued higher. In the next few paragraphs both nominal values and discounted values (present values) are shown. Note that the discounted value in 2018 is always higher than the nominal value.

²⁹⁶ See for instance: European Commission, DG REGIO, *Guide to cost-benefit analysis of investment projects, Economic appraisal tool for Cohesion Policy 2014-2020*, December 2014, p. 55.

slightly different from the discount rate used by NICE as the standard discount rate in the cost-utility analyses as part of health technology assessment reports (3.5%), of which use was made in the analyses for this report. In the sensitivity analysis, the impact of the discount rate on the results of the analysis was assessed.

The scope of the analysis was the EU28, so costs and benefits were assessed based on the actual accessibility of orphan medicines and realised sales in these markets only.²⁹⁷

F5.2 The main steps in the analysis

The evaluation has, as far as possible, been carried out in accordance with EU CBA guidelines.²⁹⁸

The main steps in the analysis were:

1. Establishment of the **impact** of the EU Orphan Regulation (i.e. the difference between the situation with EU Orphan Regulation in terms of availability of orphan medicines and the **comparator** situation). This estimate is based on analyses of the IQVIA-database;
2. Translation of the impact on accessibility, as found in the previous step, into extra **sales volumes and extra use** of orphan medicines in the EU, resulting in extra turnover for industry. This extra turnover can be directly attributed to the EU Orphan Regulation. For this step, sales data for orphan medicines in the EU, as derived from the IQVIA database, as well as the results of the analysis of the economic value of the market exclusivity reward (see Section F4 above) were used;
3. Assessment of the impact of extra use of orphan medicines on **health care costs**, based on available literature.
4. Analysis of the **health impact on patients** with rare diseases due to the treatment with the extra orphan medicines, using data from HTA reports;
5. Additional analysis concerning the division of health care costs between public and private **financing** sources, based on Eurostat data;
6. Assessing the impact of extra use of orphan medicines on **non-health costs of disease**, based on literature review.

Below the various steps are described in more detail.

Step 1. Establishing the impact, comparator situation

²⁹⁷ As besides EU countries the IQVIA database only contains information Norway data reflecting EEA and EU28 are almost, albeit not wholly identical. As described in Part A of this Appendix, the IQVIA database does not include Cyprus, Malta and Denmark giving a coverage of 25 out of 28 Member States. Furthermore, for some of these Member States the data are not complete (i.e. for The Netherlands, Latvia, Greece, Estonia and Luxembourg). The analysis has not been corrected for these missing data.

²⁹⁸ See European Commission, Better Regulation Toolbox, Tool 52, Methods to Assess Costs and Benefits. 2017; European Commission, *Guide to Cost-Benefit Analysis of Investment Projects*, December 2014.

Societal costs and health impacts can be assessed by comparing two situations: (1) the situation with the EU Orphan Regulation and (2) the situation without the EU Orphan Regulation. The situation with the EU Orphan Regulation is the situation that actually took place, as evidenced by marketing authorisations, sales data, etcetera. Since the situation without the EU Orphan Regulation is hypothetical and did not take place, an appropriate “counterfactual” or “comparator” situation needs to be constructed.

As the econometric analyses necessary to come to a counterfactual situation that satisfies the requirements in the Better Regulation Toolbox were not possible²⁹⁹, a **comparator situation** was established. This was done by assessing the **most likely impact** of the EU Orphan Regulation, relative to an extrapolated expected baseline in the hypothetical absence of the Regulation. This baseline was defined *ex post* as no *ex ante* impact assessment was conducted at the time the Regulation was introduced. Neither the interviews carried out, nor the survey results provide firm evidence of the size of such impacts. Therefore, various quantitative analyses were conducted to assess the most likely size of these impacts.

In our analysis, we assessed four types of (potential) impacts of the EU Orphan Regulation:

1. **Development of new orphan medicines**, as a result of the four incentives provided by the EU Orphan Regulation. This analysis focussed on the impact that the EU Orphan Regulation has had on research, development and marketing of new medicines for rare diseases. These new orphan medicines would not have been developed if the incentives would not have been available;
2. **Faster introduction** of orphan medicines in the EU, mainly due to the market exclusivity reward. This impact relates to the group of orphan medicines that would still have been developed without the EU Orphan Regulation, so excluding the impact as described in the previous point;
3. **Wider availability** of orphan medicines in the EU, due to the central marketing authorisation. This impact similarly only relates to the group of orphan medicines that would still have been developed even without the EU Orphan Regulation;
4. **Higher sales prices** of orphan medicines during the period of the market exclusivity reward. As shown in part 4, the market reward provided by the EU Orphan Regulation extends the period in which orphan medicines are protected from competition, thereby giving the opportunity to producers to realise non-competitive prices during this period.

The impacts were assessed as follows.

1. Development of new orphan medicines

²⁹⁹ The required econometric analysis requires the construction of a control group with similar size, containing centrally marketed medicines used for low prevalence diseases, not being orphan medicines. For this control group sales data would need to be available for a similar period. Constructing such a control group is not possible as there are not sufficient medicines available with such characteristics.

The interviews and surveys carried out in the context of this study indicate that market parties are of the opinion that the EU Orphan Regulation has indeed stimulated the development of orphan medicines. New products have been developed and brought to the market that otherwise would not have become available. However, the interviews and survey data do not reveal what part of the 131 orphan medicines that effectively became available during 2000-2017 can be attributed to the rewards provided by the EU Orphan Regulation. As part of the assessment of effectiveness, the available data was analysed to come up with a best estimate of this impact.

Ideally, the analysis would have used company data on R&D costs, production and marketing costs, pricing and revenues from individual products. Such information could show how these factors influence the decisions of companies to start or continue the development process of new orphan medicines, and how the rewards (public research, protocol assistance, fee waivers, market exclusivity) influence these decisions. Unfortunately, such information is scarce and not sufficiently available in the public domain to model the decision-making process.

Therefore, this study analysed the trend in development of new (orphan medicines) medicines as evidenced by the marketing authorisations in the EEA. This analysis is a basic statistical analysis of the number of marketing authorisations for orphan medicines as compared to those for non-orphan products.

The reasoning behind this analysis is as follows. The impact of the EU Orphan Regulation in stimulating development was not yet visible in the marketing authorisations in the first few years after it came into force, as development of orphan medicines takes substantial time. However, the impact would become more and more visible over time as the EU Orphan Regulation is likely to have stimulated new development, resulting in new marketing authorisation. Assuming a development time of 10 years or more³⁰⁰, it may be expected that the impact of the EU Regulation on development decisions for new products has become noticeable only (well) after 2000. Decisions for development of products that were introduced in the early years are not likely to have been influenced by the rewards of the EU Orphan Regulation.

For this trend analysis, the following data were used on marketing authorisations for orphan medicines.

Table 32 Number of Marketing authorisations for orphan and non-orphan medicines in EEA

Year	Orphan medicines	Non-orphan medicines	Year	orphan medicines	Non-orphan medicines
2000	0	42	2009	9	108
2001	3	29	2010	4	47
2002	4	35	2011	6	81

³⁰⁰ See e.g. EFPIA (2017), *The Pharmaceutical Industry in Figures, Key data 2017*: "by the time a medicinal product reaches the market, an average of 12-13 years will have elapsed since the first synthesis of the new active substance."

2003	5	19	2012	10	47
2004	6	28	2013	7	72
2005	4	20	2014	14	67
2006	9	42	2015	13	80
2007	13	45	2016	15	66
2008	6	60	2017	14	78

The pattern in new marketing authorisations for orphan medicines is upwards but fluctuates. The upward trend can be seen from the average numbers of marketing authorisations in the three periods of six years, being 3.7 in 2000-2005, 7.8 in 2006-2011 and 12.2 in 2012-2017.

Part of this increase may be attributable to the EU Orphan Regulation, but part of this may also be due to a general trend in development of medicines. This trend has been approximated by the number of positive opinions by EMA on non-orphan medicines in the same periods.

Table 33 Average number of new marketing authorisations

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: own analysis EMA data

Comparing these numbers, it can be concluded that the growth in marketing authorisations for orphan medicinal products in 2006-2011 was in line with the 'market trend'. From 2012 onwards, the growth has been stronger than this trend. Given the lead time involved in developing (orphan) medicines, this could well reflect the stimulating effect of the EU Orphan Regulation. Using the above data, the extra development of orphan medicinal products in 2012-2017 is assessed as follows:

- if development of orphan medicines would have been in line with non-orphan medicines ("the market"), the average number of marketing authorisation for orphan medicinal products would have been $107\% \times 7.8 = 8.4$;
- The extra development is assessed as the difference between actual and expected average number, i.e. $12.2 - 8.4 = 3.8$ products per year;
- This gives a total extra volume of 22.8 orphan medicinal products during these 6 years (i.e. $6 \times 3.8 = 22.8$);
- As some products have been withdrawn after authorisation, a correction is needed of $131 / 142 = 92\%$. This results on extra development of $22.8 \times 92\% = 21$ orphan medicinal products (rounded).

Additional analyses using linear or exponential trends in development of these products result in slightly different levels of impact, with 18 to 24 new orphan medicines being developed as a direct result of the EU Orphan Regulation.

Taking an impact of 21 newly developed orphan medicines as a result of the EU Orphan Regulation implies that 21 of the 131 orphan medicines would not have been available without the regulation, while the other 110 would otherwise still have been available. This means a relative impact of almost 20% ($21/110 = 19\%$).³⁰¹

As this statistical analysis does not take into account the decision-making variables, available information was used to check the plausibility of the finding. This check is based on the impact of the market reward on the expected sales and return on investment, and therefore on the decision to invest. It follows the reasoning that the extra protection derived from the market exclusivity reward increases the (expected) revenues from an R&D investment. Higher expected revenues imply a higher expected return on investment, and therefore a higher probability that a particular R&D project will be started or continued. This, in turn, will result in a higher probability of a successful development and market introduction.

The extra protection provided by the market exclusivity reward of the EU Orphan Regulation has been used as the defining factor in this analysis. The level of additional protection has been assessed based on the data reported in section 5.6, which shows that 48% of the orphan medicines were still protected by a patent or SPC at the end of the market exclusivity period granted by the EU Orphan Regulation, while 70% of orphan medicines were protected at the start of the market exclusivity period. This implies that in 30% of the cases, the effective extra protection granted by the market exclusivity is indeed the full 10 years, while in 48% of the cases there is no extra protection, as patents or SPCs were still valid at the end of the market exclusivity period. The remaining 22% have an average additional protection period of 2.25 years (see Section 5.6). The average effective extra protection from competition that the market exclusivity reward of the EU Orphan Regulation offers is estimated at 3.4 years.

These 3.4 years imply an extension of the period in which the product is protected from competition, on top of protection provided by patents / SPCs. It should be noted also that the protection offered by market exclusivity is different from that offered by patents or SPCs. Whereas the latter protect only against products with the same active substance and for the same indication (generic or biosimilar products), market exclusivity protects more broadly against all products that are considered 'similar'. Moreover, even if a sponsor develops a product that is not similar to an existing orphan medicine that is under market exclusivity, it will need to demonstrate significant benefit over the existing product before it could be authorised as an orphan medicine. The value of this added layer of protection over that offered by a patent or SPC could, however, not be established.

This extra protection is on top of the protection provided by patents / SPCs. The relative size of this extra protection clearly differs per situation. The

³⁰¹ This method assumes that all extra development (i.e. above the normal market trend) can be attributed to the EU Orphan Regulation. However, there may have been other developments stimulating the development of orphan medicines, such as supply side efficiencies (e.g. technological advances in genome analyses). There might thus be some overestimation of the impact (not a conservative, but rather a 'liberal' assessment of the impact).

effective duration of the protection by patent/SPC may vary per situation and can be less than 20 years. Using an average effective protection period by patents/SPCs of 15 to 20 years, the additional protection period realised by the market exclusivity reward can be estimated at ranging from $(3.4/20=)$ 17% up to $(3.4/15=)$ 23 %.³⁰².

This additional protection implies that during this period, extra revenues can be generated for the newly developed orphan medicine (compared to a situation without the EU Orphan Regulation). The size of these extra revenues depends on (a) the market on which the orphan medicines is introduced, and (b) the price policy applied by the producer. Also, here a variety of situations can apply. For the purpose of illustration, assume that the product is introduced at the same time in major markets such as EU and US and a same price level would be achieved, the EU market protection may result in 50 to 60% extra revenues if relative pharmaceutical market sizes or relative populations are taken as the basis.³⁰³ Using these values, the extra revenues due to the market exclusivity reward would amount to $50\% \times 17\% = 8.5\%$ to $60\% \times 34\% = 20.4\%$.

In summary, these data suggest that the market exclusivity reward may result in a 10 to 20% increase in revenue potential for an average orphan medicine. The extra potential is higher for orphan medicines that benefit from the full 10 years extra protection, or lower if the market exclusivity period overlaps with the patent / SPC protection.

A higher revenue potential is likely to increase the attractiveness of a development process, and thus may result in higher probability for positive decisions and thereby on higher development results. The relation between such a decision and revenue potential is however not known. Nevertheless, given the higher revenue potential for an average orphan medicine of 10 to 20%, the impact found in the trend analysis (20% extra development) is deemed plausible.

In summary, it is assessed that the average number of additional orphan medicines having been developed as a direct result of the EU Orphan Regulation amounts to 21 (out of the total of 131). There is, however, quite some uncertainty around this estimate. Therefore, in the reference analysis an impact of 21 orphan medicines is used, while sensitivity analyses have been carried out with a lower estimate of 18 extra orphan medicines and a higher estimate of 24 extra orphan medicines.

2. Faster availability of orphan medicines in the EU market

Given the combination of rewards (fee waiver, protocol assistance, market exclusivity), the EU Orphan Regulation may not only have stimulated new development of orphan medicines, but may also be expected to have

³⁰² In this calculation, it is assumed that the level of protection from competition derived from market exclusivity is equal to the protection derived from patents/SPCs. This may be an underestimation of the effective protection as the market exclusivity reward may give a stronger protection as it concerns "similar" products.

³⁰³ The EU share in the combined population of EU and US is approximately 60% (rounded), while it's share in the total pharmaceutical market is roughly 50% (based on sales data for 2014 as published by EFPIA).

stimulated that orphan medicines which would also have been developed without the regulation (within or outside Europe) became *faster* available in the EU market.

To assess this potential impact of the EU Orphan Regulation, the following analyses were carried out on the three sub-sets of medicines identified from the IQVIA-database:

- For orphan medicines, the time between the marketing authorisation date in the EEA and appearance in the first EU market was calculated. Subsequently, it was assessed in how many EU Member States the product was available exactly three years after the marketing authorisation date.
- For orphan-likes a similar assessment was made by calculating the time between the marketing authorisation date in the US and the appearance in the first EU market. Subsequently, it was assessed in how many EU Member States the product was available exactly three years after the marketing authorisation date.

In this context, it should be noted that it is likely that there is a “*survivor bias*” in the group of orphan-likes as defined from the IQVIA database, due to the fact that only those products that were at least selling in the first quarter of 2008 are visible in the IQVIA database. Orphan-likes that left the EU market(s) prior to 2008, could not be included. The analysis thus only includes the “*survivors*” which are likely to have reached the first EEA/EU market earlier and have been launched in more EEA/EU markets. Moreover, all orphan-likes were sold throughout the period 2008-2016. Given this survivor bias, the found impact is a conservative estimate.

A second remark on the comparison of finding for the orphan-likes and orphan medicines is that the orphan-like products were introduced before 2000, while the orphan medicines were introduced after 2000. The difference may thus partly be caused by a difference in timing. For this reason, the analysis for the non-orphan medicines group was carried out.

In this context, it is important to use a common comparison basis for the two groups and take the various expansions of the EU into account. We therefore limited the analysis to the ‘old’ EU-12 Member States, as they form a uniform and consistent group for the period before 1995 and the period after 1995.

- Similar to the analysis for orphan-likes, for newly developed non-orphan products, the development in the lead time between international product launch date and the appearance in the first EU market was analysed over a longer period of time (1990-2016). Also for this group, it was assessed in how many EU Member States the product was available three years after the international product launch date. This analysis was used to assess the general trend over time in the “time to market” and spread of availability.

The results of these analyses are shown in Table 34.

Table 34 Time to EU market and availability of various types of medicine

	Orphan medicines	Orphan-likes	Non-orphan medicines
<i>Before 2000</i>			
Time to market		30.2 m	15.9 m
Number of EU12 MS reached after three years		3.7 MS	2.9 MS
<i>After 2000</i>			
Time to market	1.1 m		5.2 m
Number of EU12 MS reached after three years	5.7 MS		4.2 MS

The analysis of IQVIA data shows that the average time to EU market for orphan-likes introduced in the US before 2000 (based on 70 products that actually reached the EU market) was 30.2 months.

The analysis for orphan medicines with market entry after 2000 shows that the time difference between market entry in US and EU was on average 1.1 month. The difference in time to the EU market between the two groups would thus indicate a much shorter time to the EU market for orphan medicines as compared to orphan-likes, of 29 months. However, this difference cannot be attributed to the EU Orphan Regulation only, as there may have been an overall trend of faster access of medicines to the EU market.

The analysis of the development in the lead time to EU market for non-orphan medicines in the same time period shows that it has indeed decreased, by (15.9 – 5.2=) 10.7 months between 1990-2000 and 2010-2018, or a reduction of 68%.

This means that, even without the EU Orphan Regulation, the time to the EU market for orphan-likes may have been reduced, with 68% of 30.2 months (20.3 months), to 9.9 months. The impact of the EU Orphan Regulation is thus assessed to be the difference between the hypothetical time to market of 9.9 months and the observed time of 1.1 months, thus equal to 9 months (rounded).

Based on this analysis it is concluded that for medicines for patients with rare diseases the average time to reach the EU market has become shorter since the EU Orphan Regulation came into effect, by 9 months.

3. Wider availability of medicines in EU market

In addition to stimulating faster availability, the EU Orphan Regulation may also be expected to have stimulated more widely availability of orphan medicines which would also have been developed without the Regulation (within or outside Europe) in the EEA/EU market. With respect to the wider availability, the analysis shows that three years after marketing authorisation

in the US market, the orphan-likes were on the market in on average 3.7 of the EU12 markets, while orphan medicines were generally available in on average 5.7 EU12 markets after three years. So, three years after market introduction orphan medicines were available in 2 more Member States (out of 12).

A similar exercise based on the international product launch dates for non-orphan medicines shows that the typical market coverage for other medicines has also increased, from 2.9 to 4.2 Member States (of EU12) after three years, or by 45% in the same period. If we adjust the geographical extension evident among orphan medicines in light of the underlying trend of improving market availability for all medicines, we arrive at an expected market coverage of $145\% \times 3.7 = 5.36$ MS. As the actual spread shows 5.7 Member States, the additional impact of the EU Orphan Regulation can be estimated 0.34 additional Member States of the EU12 (or 3%).

This finding needs to be translated to the EU28 level. In doing so, two observations are relevant³⁰⁴:

- The potential size of the markets based on population (the EU28 being approximately 33% larger than EU12)³⁰⁵;
- The availability of orphan medicines which is generally lower in EU16 as compared to EU12, as can be seen from data presented in Chapter 5. Based on actual spread of orphan medicines, it is calculated that availability in the EU16 is generally at 65% of the level of the EU12.³⁰⁶

Taking this into account, the impact of the EU Orphan Regulation on the geographic spread of orphan medicines after three years can be estimated at 3% for the EU12 (or 11.5 million inhabitants) + 3% * 65% for EU16 (or 2.5 million inhabitants). This translates to an average impact for EU28 of 2.7%, or 14 million inhabitants of EU28. This equals the population of Belgium and Lithuania.

4. Higher sales revenues of orphan medicines due to market exclusivity reward

A fourth potential impact of the EU Orphan Regulation concerns the potential higher sales revenues as a result of the longer period of market protection

³⁰⁴ The corrections are made to translate the finding for EU12 to the level of EU28. It reflects the situation that population of the EU16 member states is generally smaller than that of EU12 member states, which gives a smaller patient basis. It also reflects that situation that in EU16 there are fewer orphan medicines on the market. Both factors make that the impact for EU28 is smaller in relative terms than for EU12. In the calculation the impact in % terms is used to calculate the effect. The translation of this percentage in number of Member States is only for illustration purposes. In interpreting this number one should envisage a (hypothetical) average EU Member State with 18.3 million inhabitants.

³⁰⁵ The calculation is based on the population data per 1.1.2017 as published by Eurostat. <https://ec.europa.eu/eurostat/documents/2995521/9063738/3-10072018-BP-EN.pdf/ccdfc838-d909-4fd8-b3f9-d60d65ea457f>

³⁰⁶ Present accessibility in the eight EU-12 countries is 93,25 orphan medicines; in the 12 EU-16 member states it is 60,75 orphan medicines. The ratio thus becomes $60,75/93,25=65\%$. However, as accessibility in EU16 will increase over time, using present day accessibility results in a somewhat conservative estimate of the impact.

through the market exclusivity reward. For this impact, the result of the economic valuation of the market reward as described in Section F4 of this Appendix is relevant. That analysis shows that, for the four orphan medicines for which the approach could be applied the economic value is estimated at 12 to 54% of the total sales revenues realised for the orphan medicines (average 30%). However, the reward is on top of other protections, meaning that the effective extra protection varies from 0 to 10 years at orphan medicine level, with an average of 3.4 years for the whole group of orphan medicines. The impact of the EU Orphan Regulation on sales is thus assessed to be that all orphan medicines that received a marketing authorisation realise extra revenues from orphan medicine sales during the last 3.4 years of their market exclusivity period. This benefit relates to 64 orphan medicines (active and expired) during the period 2000-2017³⁰⁷.

This assessment implicitly assumes that even though not all orphan medicines experience generic entry, there is still additional value realized due to the market protection, as sponsors set their prices not knowing beforehand whether competition will arise. We deem this to be a reasonable assumption, even though the methodology used does not allow to assess this assumption for situations in which no competition has arisen. An alternative assumption, however, would be that competition only emerges for those products with a relatively high profit margin. In that case the extra reward would only be realised by a part of the orphan medicines.

In the sensitivity analysis it is assessed to what extent the result is affected if the extra revenues are only calculated for part of the orphan medicines (i.e. for 44% of the relevant orphan medicines as found in our analysis of 16 orphan medicines in section F4).

Summary of impact of EU Orphan Regulation

Summarising the above analyses, it is concluded that the most likely impact of the EU Orphan Regulation is that:

- Out of the 131 relevant orphan medicines (active and with expired marketing authorisation), between 18 and 24 orphan medicines have been developed extra (input for baseline analysis: 21 orphan medicines) as a direct result of the regulation;
- The remaining 107 to 113 orphan medicines were on average 9 months earlier available than would have been the case without the EU Orphan Regulation;
- That this same number of orphan medicines were on average available to 14 million more EU28 inhabitants (2.7% of population) after three years, than without the EU Orphan Regulation. This implies that each orphan medicine became available to more patients, comparable to the patients in Member States of Belgium and Lithuania;
- Due to the market exclusivity reward, producers of orphan medicines were able to realise a higher price, which is equivalent to 12 to 54% of

³⁰⁷ The other orphan medicines had not yet reached the 6.56 years of market exclusivity at the end of 2017.

the revenues (input for baseline analysis: 30%), during, on average, the last 3.4 years of their market exclusivity period.

Step 2. Translation of impact of EU Orphan Regulation into increased accessibility of orphan medicines

The next step in the CBA involves the translation of the impact into higher accessibility of orphan medicines in 2000-2017 in the EU market. Note that the first three impacts described above result in higher accessibility (and higher sales volumes) of orphan medicines. In order to translate the combined accessibility effect of these three impacts into sales, the average annual sales revenues of active orphan medicines³⁰⁸ during 2008-2016 has been used, estimated at € 67 million (in current prices).

The fourth impact described above does not result in higher accessibility/sales of orphan medicines, but has the effect of higher prices and thus higher revenues for the industry without affecting the accessibility of orphan medicines.

Step 3. Assessing impact on health costs

The higher use and higher prices of orphan medicines that can be attributed to the EU Orphan Regulation result in higher treatment costs for patients, which in turn affects total health care costs. The exact impact on health care costs differs per type of rare disease, and because of differences in the additional requirements of the treatment, as well as the savings in health care costs for alternative treatments. This information is to a certain extent available from HTA- reports on orphan medicines.

In order to assess this impact on health care costs, as well as to assess the health impact for patients suffering from rare diseases, available HTA reports for orphan medicines were screened. A thorough review was carried out to assess the availability of this type of information within the HTA reports for orphan medicines, as available in the public database of University of York Centre for Reviews and Dissemination and a list of HTA reports supplied by EMA. For a total of 50 orphan medicines that received marketing authorisation in the EEA a HTA report was found. However, not all of these reports proved useful to establish the impact on health costs and the health impact for patients. **Table 35** provides an overview of the available information in the identified HTA reports.

³⁰⁸ Active orphan medicines are those for which the market exclusivity period had not yet expired and which were not withdrawn.

Table 35 Overview of HTA reports with economic information

Contents of reviewed HTA reports	No. of reports
Limited /no economic information	10
No information on cost effectiveness	8
Insufficient information given (e.g. ICER given, but no treatment cost)	5
Information on ICER and cost of treatment, but no health impact / patient	14
Information on ICER and health impact per patient (in QALY)	8
Information on ICER, health impact per patient and cost of treatment	5
Total	50

Source: own elaboration. ICER stands for 'Incremental Cost Effectiveness Ratio', which is the ratio of the change in the cost of a therapeutic intervention (i.e. use of the orphan medicine) compared to the alternative/current treatment.

The review of HTA reports shows that only a small minority of these reports contains full economic information, such as costs of treatment with the orphan medicine per patient (per year), costs for the alternative (comparator) treatment of the patients suffering from the rare disease and the health impact for patients. A larger number of reports contains conclusions on the Incremental Cost Effectiveness Ratio (ICER) analysis, which relates the (discounted) additional costs for the health system to the number of quality adjusted life years (QALYs) gained.³⁰⁹ From the list of 50 reports, a selection of 32 reports has been made which could be used for the assessment of health impact of use of orphan medicines (see table below). The basis for assessment of the total impact on health costs was not strong enough, though.

Table 36 List of 32 orphan medicines used in the evaluation of costs and health benefits at Regulation level

OMP	Source
Adcetris	https://www.nice.org.uk/guidance/ta478/documents/final-appraisal-determination-document
Arzerra	https://www.nice.org.uk/guidance/ta202/resources/chronic-lymphocytic-leukaemia-ofatumumab-final-appraisal-determination3
Blincyto	https://www.nice.org.uk/guidance/ta450/documents/final-appraisal-determination-document
Bosulif	https://www.nice.org.uk/guidance/ta401/documents/final-appraisal-determination-document
Bronchitol	https://www.nice.org.uk/guidance/ta266/documents/cystic-fibrosis-mannitol-final-appraisal-determinaton3
Cyramza	https://www.nice.org.uk/guidance/ta378/documents/final-appraisal-determination-document

³⁰⁹ For more information on QALY see for instance: MacKillop & Sheard, 2018, Quantifying life: Understanding the history of Quality-Adjusted Life-Years (QALYs), Social Science and Medicine, volume 211

OMP	Source
Esbriet	https://www.nice.org.uk/guidance/ta504/documents/final-appraisal-determination-document
Exjade	NHS Worcestershire, DEFERASIROX IN THE TREATMENT OF TRANSFUSIONAL IRON OVERLOAD IN THALASSAEMIA MAJOR AND OTHER ANAEMIAS
Fabrazyme	https://www.ncbi.nlm.nih.gov/books/NBK62284/
Farydak	https://www.nice.org.uk/guidance/ta380/documents/final-appraisal-determination-document
Glivec	https://www.nice.org.uk/guidance/ta70/resources/guidance-on-the-use-of-imatinib-for-chronic-myeloid-leukaemia-pdf-2294751800005
Holoclar	https://www.nice.org.uk/guidance/ta467/documents/final-appraisal-determination-document
Iclusig	https://www.nice.org.uk/guidance/ta451/documents/final-appraisal-determination-document
Imbruvica	https://www.nice.org.uk/guidance/ta502/documents/final-appraisal-determination-document
Imnovid	https://www.nice.org.uk/guidance/ta427/documents/final-appraisal-determination-document
Jakavi	https://www.nice.org.uk/guidance/ta386/documents/final-appraisal-determination-document
Kalydeco	https://www.nice.org.uk/guidance/ta398/documents/committee-papers-2
Kyprolis	https://www.nice.org.uk/guidance/ta457/documents/final-appraisal-determination-document
Lartruvo	https://www.nice.org.uk/guidance/ta465/documents/final-appraisal-determination-document
Lenvima	https://www.nice.org.uk/guidance/gid-ta10101/documents/assessment-report
Lynparza	https://www.nice.org.uk/guidance/ta381/documents/final-appraisal-determination-document
Ninlaro	https://www.nice.org.uk/guidance/ta505/documents/final-appraisal-determination-document
Nplate	https://www.nice.org.uk/guidance/ta221/resources/romiplostim-for-the-treatment-of-chronic-immune-idiopathic-thrombocytopenic-purpura-pdf-82600305088453
Ocaliva	https://www.nice.org.uk/guidance/ta443/documents/final-appraisal-determination-document
Ofev	https://www.nice.org.uk/guidance/ta379/documents/final-appraisal-determination-document
Revlimid	https://www.nice.org.uk/guidance/ta322/documents/myelodysplastic-syndrome-deletion-5q-lenalidomide-id480-final-appraisal-determination-document2
Revolade	https://www.nice.org.uk/guidance/ta293/documents/thrombocytopenic-purpura-eltrombopag-rev-ta205-final-appraisal-determination3
Somavert	NHS Worcestershire, THE USE OF PEGVISOMANT (SOMAVERT®▼) IN THE TREATMENT OF ACROMEGALY

OMP	Source
Spinraza	https://www.zorginstituutnederland.nl/publicaties/adviezen/2018/02/07/pakketadvies-nusinersen-spinraza-voor-de-behandeling-van-spinale-musculaire-atrofie-sma
Sprycel	https://www.nice.org.uk/guidance/ta426/resources/dasatinib-nilotinib-and-imatinib-for-untreated-chronic-myeloid-leukaemia-pdf-82604667051205
Strimvelis	https://www.nice.org.uk/guidance/hst7/documents/final-evaluation-determination-document
Ventavis	https://www.nice.org.uk/guidance/gid-tag382/documents/schering-health-care-ltd2

Due to the limited availability of data in the HTA reports, the impact on total health care costs other could not be assessed with sufficient reliability. Evidence at orphan medicine level suggests that the total impact on health care costs could either be higher than the costs of orphan medicines, or lower than the costs of orphan medicines, but it was not possible to make an assessment at the level of the whole group orphan medicines. Therefore, it has been assumed that the impact of the EU Orphan Regulation on health care costs equals the extra sales revenues generated by industry due to the higher accessibility and higher prices (all four impacts) as calculated in step 2.

In addition to the health care costs related to treatment with the orphan medicines, there may be a future effect on health care costs, which is not shown in the HTA reports. For instance, if treatment with orphan medicines is successful in combatting the rare disease, the cured patient may contract another disease later in life. This effect could not be taken into account, which means a potential underestimation of the health care costs.

Step 4. Assessing health benefits

Using the estimation of extra health care costs due the use of orphan medicines (as described in step 3), the information on the ICERs can be used to assess the health impact on patients suffering from rare diseases.

The health benefits are expressed in terms of the number of QALYs realised by patients. There is much debate on the extent to which such benefits can be expressed in monetary terms and, if so, what value should be applied. Given these discussions and the diverging views on the applicable value, no value has been applied in the CUA. Instead, the absolute number of QALYs is presented as the health impact, which will be related to the total societal costs.

In order to calculate the health impact in terms of QALYs, the extra health care costs incurred are translated into QALYs by using information on the ICERs from HTA reports. As indicated, ICERs were available for 32 orphan medicines. This group includes reports for 5 orphan medicines that were prematurely withdrawn and 3 orphan medicines for which no sales have been recorded in 2008-2016. The following overview excludes information from these eight reports. The ICERs for the remaining 24 products differ considerably across orphan medicines, ranging from €23,000 / QALY to nearly

€1 million / QALY. The table below gives a summary. The average ICER for this group is €110,000, the median being between €55,000 and €59,000.

Table 37 Overview of ICER of Orphan Medicinal Products that received Marketing Authorisation

ICER	Number of orphan medicines
< €40,000 per QALY	6
€40,000 to €80,000 per QALY	11
€80,000 to €120,000 per QALY	4
> €120,000 per QALY	3
TOTAL	24

In calculating the average ICER (€110,000) of each of the 24 orphan medicines is given the same weight. However, some orphan medicines are more widely used than others, which implies that the realised cost effectiveness may be different from this average. To investigate this, a weighted average was estimated for the individual years 2008-2016. This was done by taking only the ICERs the active orphan medicines for the individual years and subsequently using the turnover of the individual orphan medicines as the relative weights. This estimation resulted in a weighted average annual value in the range of €48,000 to €60,000 per QALY; the average over the years being €54,000.³¹⁰

The weighted average ICER is substantially lower than the non-weighted average ICER presented above. This implies that, while many orphan medicines are generally expected to deliver health improvements at relatively high costs, those that are actually reimbursed are generally more cost effective. It should be noted, however, that the applied method of weighing has a disadvantage in that it uses total sales of a product, including sales of products relating to non-orphan indications. Hence, the presented weighted average ICER may be an underestimation as high sales of products with multiple indications may distort the average.

The above finding, that in practice use of the cost effective orphan medicines is higher than those of less cost effective medicines, is in line with a recent paper by Berdud, Drummond and Towse (2018). They estimate the average ICER for orphan drugs appraised by SMC and NICE to be around £70,000, while the average ICER of (7) orphan drugs with positive recommendations by both organisations is assessed to be substantially lower, at around £45,000, or approximately €60,000.

In order to assess the health impact of the EU Orphan Regulation, a wide range has been applied for the ICER (€54,000 to €110,000). There are several reasons for this. First, the above analysis shows that there is a wide variation in the results of the different approaches, each having disadvantages. Second, almost all the publicly available HTA reports relate to the situation in

³¹⁰ The share of these orphan medicines in total turnover of active orphan medicines ranges from 35-60% in these years, as reported in the IQVIA database.

the United Kingdom (UK). This situation may not be representative for the situation in other EU28 Member States. For instance, the cost difference between treatment with orphan medicine and the comparator treatment in other Member States may be quite different from that in the UK for various reasons: differences in orphan medicine pricing between Member States, differences in applied comparator treatments (notably as a result of differences in labour costs). Third, for many orphan medicines no HTA report containing an analysis of the ICER could be found. It is therefore not known to what extent the available ICERs are representative for the whole group of orphan medicines that are being used in the EU.

Given these observations there is sufficient reason to use a relatively wide range for the ICER in the CUA, in particular as this variable is an important driver for the outcome of the analysis.

Step 5. Financing of health costs

Part of the additional health care costs are reimbursed from collective sources (either government budgets, collective health insurance systems or otherwise). Healthcare systems across the EU Member States are organised and financed in different ways. Eurostat reports on healthcare expenditures and financing at regular intervals. For instance, the online publication *Healthcare expenditure and statistics* of March 2018³¹¹ presents the healthcare expenditures by financing scheme for all Member States (except Malta). It shows that household out-of-pocket payments are an important source of health care funding in many Member States, accounting for nearly 7% of total expenditures in France to almost 50% in Bulgaria (the average for EU being 21%).³¹² In addition, voluntary health insurance schemes are used to finance health care costs. Taking these two sources of financing together, the private share in expenses can be estimated to range from 16% in Germany to 57% in Cyprus (EU average being 27%). The remainder is financed from either government budget or compulsory insurance or savings schemes.

In addition, in this study's survey of national public authorities, we found that:

- In the vast majority of responding Member States (17 of 20, or 85%), the reimbursement mechanism for orphan medicines is the same as for non-orphan medicines;
- In the majority of Member States (15 out of 20, or 75%), financing of orphan medicines occurs through the national health service. In a minority of cases (6 out of 20, or 30%) financing is also partly derived from the health insurance system;

³¹¹ European Commission, see: <https://ec.europa.eu/eurostat/statistics-explained/pdfscache/37773.pdf>.

³¹² The report describes the average division of health care costs between private and public payers. It shows substantial variation between the EU Member States in the division of healthcare expenditures between public and private payers. For orphan medicine related expenditures the division may, of course, be different, as this concerns marginal expenditures for in some cases very costly treatments.

- None of the responding Member States has a separate fund for financing of orphan medicines, nor is the voluntary insurance involved;
- For six Member States (30%), out-of-pocket payments for orphan medicines are also recorded.

Based on this, it can be concluded that only a small proportion of costs related to orphan medicines is financed from out-of-pocket expenses by patients, most likely less than 5% of the total. The reasoning is as follows: in 30% of the Member States out-of-pocket payments is a source of financing of costs of orphan medicines. On average such payments cover 21% of costs of the health care system. The approximate share of out-of-pocket payments could thus be $30\% \times 21\% = 6\%$. As treatment with orphan medicine is costly, it is very likely that private contributions are capped through various cost exemption schemes and are far less than the average contribution, so less than 6%. For the present analysis, a level of 50% is assumed, so $50\% \times 6\% = 3\%$. Consequently in the CBA a 97/3 division has been used between public and private financing.

Step 6. Impact on other costs of disease

The societal costs of a disease are wider than those borne by the health system. Examples of non-health care costs of a disease are the use of social services, the costs of involvement of (professional or informal) carers outside the health system and productivity losses resulting from unplanned absences from work or early retirement by patients. Some of these costs are borne by the patients and their relatives, other costs are borne by others in society or by the government.

The level of non-health care costs depends very much on the type of disease, including characteristics such as typical patient groups (children, adults, elderly people) and the severity of the disease (life threatening or not). In addition, the impact of the orphan medicine on the level of such costs may differ from that of the alternative (comparator) treatment. For instance: the impact on non-health care costs may be quite different for an orphan medicine that has the effect of curing a disease, as compared to an orphan medicine that has the effect of reducing the burden of the disease.

Although several studies are available on the societal costs of rare diseases, there is limited information available on the impact of treatment with orphan medicines on such costs. HTA reports normally do not report on the impacts beyond the health system. This implies that any wider social impact cannot be established at the level of the EU Orphan Regulation.

F5.3 Costs and benefits by stakeholder group

This section of the Appendix presents the costs and benefits for individual stakeholder groups, based on the results from the six steps described above.

F5.3.1 Costs and benefits for Industry

The impact of the EU Orphan Regulation results in the following effects for industry:

Extra R&D costs due to extra development of orphan medicines

Firstly, the industry has incurred higher costs due to the extra development of orphan medicines. These additional costs for industry have been calculated by using the number of newly developed orphan medicines (input for baseline analysis: 21 orphan medicines) and the range of R&D costs found for orphan medicines (range €479m to €725m, see Section 8.2 of the main report; input for baseline CBA the average of this range: €602m). These cost estimates are net of subsidies received from governments and include already the cost of capital for the industry, using 11%.

As the R&D costs can potentially be spread over worldwide sales, not all of this investment needs to be allocated to the EU market. According to the turnover data presented in the main report, the average share of EU in worldwide sales of medicines for rare diseases is estimated at 21%. As this average may not be representative for newly developed orphan medicines, a more conservative approach is taken in the CUA by allocating 60% to the EU market, based on the relative population sizes of US and EU. Given these assumptions the total additional R&D costs for industry in 2000-2017 have been estimated at $21 \times \text{€ } 602 \text{ m} \times 60\% = \text{€ } 7.6 \text{ billion}$ in nominal terms.

These extra development costs have been incurred by industry in the years up to the market introduction of the additional products. In order to assess the discounted value of the extra development costs, the costs have been phased in the 10 years before the market introduction of the 21 orphan medicines. The resulting present value of this stream of costs is estimated at € 11.0 billion.

Extra sales revenues due to sales of extra developed orphan medicines

As these 21 orphan medicines are developed due to the EU Orphan Regulation, industry has realised additional turnover in relation to these newly developed products. Using the average additional turnover of active orphan medicines, additional turnover is assessed at $21 \times \text{€ } 67 \text{ mln} = \text{€ } 1.4 \text{ billion}$ per year.

The additional turnover has been taken into account for the years after market introduction of the respective orphan medicines, up to and including the year 2017. As explained, it is assumed that the impact of the Regulation has been that new products stimulated by the regulation have been introduced in the EEA/EU market from 2010 onwards. This means that at the end of the period taken into account (2000-2017) these products had been on the market for less than 10 years. Given the timing of the introduction of orphan medicines, the average number of years after introduction of these 21 orphan medicines is assessed at 4.6 years.³¹³ Total additional turnover for

³¹³ The introduction of the 21 new orphan products is assumed to be distributed over the years 2008-2017 as follows: 1,29 - 1,93 - 0,86 - 1,29 - 2,14 - 1,50 - 3,00 - 2,79 - 3,21 - 3,00 It is assumed that product are introduced at the beginning of the year.

additionally developed new orphan medicines during 2000-2017 is thus estimated at $4.6 \times \text{€}1.4 = \text{€} 6.5$ billion.

The present value of this additional turnover (in 2018 prices) is estimated at € 8.5 billion.

Extra sales revenues due to faster and wider availability of the other orphan medicines

Industry not only realised extra sales in the EU because of additional newly developed orphan medicines, but also because of the faster market introduction and the wider spread of orphan medicines after initial market entry. The extra sales due to the 9 months faster entry on the EU market are estimated by multiplying the relevant number of orphan medicines (110) by 9 months turnover ($9/12 \times \text{€} 67$ million = € 50 million), resulting in a total value of € 5.5 billion in the years 2000-2017 (nominal value).

The wider spread of orphan medicines after introduction was estimated at 2.7% of EU population. This additional coverage 2.7% of total estimated turnover in the years 2000-2017 for the 110 products and amounts to € 1.8 billion (nominal value).

The nominal value of the combined additional sales revenues for these 110 orphan medicines due to faster and wider availability is thus estimated at € 7.3 billion (€ 10.6 billion in present value terms)

Extra production costs due to extra sales

The extra sales realised by industry means that extra costs have been incurred on manufacturing, distribution and marketing of the medicines. These extra costs have been assessed on the basis of the insights from the analyses presented in Section F4. In this analysis, it is concluded that during the period in which products are protected from competition, a higher price can be realised, yielding around 30% of sales revenues. This means that the other 70% of revenues can be assumed to represent the cost items mentioned above, as well as a 'normal' profit margin as this is the price level at which generic competition is possible.³¹⁴ Therefore, it has been assumed that in order to realise the extra sales, including those of extra developed orphan medicines, the industry has incurred extra costs at 70% of the extra revenues generated.

Given that extra revenues, as described above amount to €13.7 billion (€ 6.5 billion for newly developed products, € 5.5 billion due to faster access, € 1.7 billion to wider availability), the extra production cost (including normal profit) incurred during 2000-2017 are assessed at €9.7 billion (70% of €13.7 billion) in nominal value terms (€13.4 billion in present value terms).

Extra revenues due to higher prices

³¹⁴ The analysis in F4 implies that generic competition resulted in a price drop for the four products analysed of on average 30% as compared to the price set during the market exclusivity reward. At that price level generic competition is apparently profitable. The exact profit level that is realised by generic competitors may vary per product and cannot be ascertained. The exact level of profit in a competitive situation ("normal profit margin") is not known from this analysis.

As described, on average the industry obtained an extension of the period in which orphan medicines are shielded from competition from similar medicinal products of on average 3.4 years. During this period, extra revenues are generated due to higher prices. These extra revenues are taken into account only for those (64) products which reached years 6 to 10 of the market exclusivity period in 2000-2017. As argued above, the benefits have been taken into account for all 64 products in the reference case analysis. The value of this extra turnover can be assessed by taking 30% of € 67 million during at maximum 3.4 years for 64 products. As not all 64 products were at the end of their market exclusivity period by December 2017, the effective average duration was 2.6 years. This results in extra revenues for industry at € 3.3 billion (€ 4.6 billion in present value).

Protocol assistance, fee waiver

The sector has directly benefited from the fee waiver and protocol assistance rewards under the EU Orphan Regulation. The costs for EMA associated with these rewards amounted to € 0.1 billion over the years 2000-2017 (present value € 0.2 billion).

Table 38 (below) summarises the costs and benefits for industry, based on the assessed impact of the EU Orphan Regulation and using the average estimates. It shows that the costs for industry were higher than its benefits, at around € 0.5 billion.

Various sensitivity analyses have been carried out using alternative assumptions for the various inputs used. If only one variable is changed, the following net benefit (or net cost) results:

- Number of newly developed orphan medicines 24 (instead of 21): net cost € 1.9m;
- Higher R&D costs for newly developed orphan medicines (€725m instead of €602m): net cost € 2.7m;
- Number of newly developed orphan medicines 18 (instead of 21): net benefit € 0.9m;
- Lower R&D costs for newly developed orphan medicines (€725m instead of €602m): net benefit € 1.7m;
- Market exclusivity reward for only 44% of orphan medicinal products (instead of for all): net cost € 6.3m;
- Wider spread of orphan medicines 5% (instead of 2.7%): net benefit € 0.0m.

The upper and lower estimates for inputs in the analysis have also been combined. The table presents the results of a combination of the upper and lower estimates which given the most extreme outcome for industry. The "pessimistic" estimate combines the higher development costs, the higher (number of newly developed orphan medicines, the lower value for market exclusivity and a market exclusivity reward for only part (44%) of the orphan medicines. The "optimistic" estimate combines the values at the other end of the uncertainty range. The results of the sensitivity analyses are given as a range in the lower line of the table.

The general conclusion from the sensitivity analysis is that no robust conclusion can be drawn as to whether industry has experienced a net benefit

or a net cost due to the EU Orphan Regulation in 2000-2017. In interpreting this conclusion, it should be kept in mind that the R&D costs already include a provision for the cost of capital used in the development process, based on an remuneration of 11%. It further reflects that investment for new orphan medicines have been made that have only been on the market for a limited number of years and are still within the period of market exclusivity. There is thus potential for industry to increase net benefits in the years after 2017, even if no new orphan medicines would be developed.

Table 38 Industry Costs and Benefits, due to the Orphan Regulation, 2000-2017 (discounted value 2018, prices 2018, in € billions)

Effect	Costs	Benefits
R&D costs associated with the additional orphan medicines (EU part)	-/- €11.0b	
Sales revenues of additional orphan medicines in EU		€19.1b
Extra costs of manufacturing, marketing, distribution in EU including extra "normal profit"	-/- €13.4b	
Extra revenues due to ME reward		€4.6b
Cost saving due to protocol assistance and fee waivers		€0.2b
Total	-/- €24.4b	€23.9b
NET BENEFIT (COST)	(€ 0.6b)	
Range Net Benefits (minimum – maximum) a)	-/- €11b to +€11b	

a) In the minimum scenario the higher R&D costs are combined with low effects on orphan medicine development and R&D compensation. In the maximum scenario opposite assumptions are used.

F5.3.2 Costs and benefits for Health care sector

The impact of the EU Orphan Regulation on the health care sector is two-fold.

Firstly, due to the additional use of orphan medicines the costs of treating patients have increased with the costs of the orphan medicines. There may be additional impacts on health care costs (additional costs of treatment with orphan medicines, savings on costs of alternative treatments), but such impacts could not be assessed.

Secondly, the health care sector will be compensated for these higher costs, from public and private sources. The revenues have thus increased, by the same amount as costs have risen.

This results in the following costs and benefits due to the EU Orphan Regulation for the health sector.

Table 39 Costs and Benefits due to the Orphan Regulation for the health sector, 2000-2017 (discounted value 2018, prices 2018, € billions)

Effect	Costs	Benefits
Extra costs due to treatment with orphan medicines	-/- €23.7b	
Additional extra costs due to new treatment	NDA a)	

Savings in costs of alternative treatment		NDA a)
Public and private financing		€23.7b
TOTAL	-/-€23.7b	€23.7b
NET BENEFIT		€0.0

a: NDA: not sufficient data available to assess this effect

The total extra costs have been estimated at nearly €24b. The range of uncertainty for this estimate is smaller than for industry. Using the same combinations of assumptions in the as for industry, the sensitivity analysis shows a range of possible outcomes from a net cost of €20b to € 27b.

F.5.3 Costs and benefits for Governments

The stakeholder group, 'governments and public organisations,' contains various types of governmental organisations, including national governments, the EMA, the European Commission and public or semi-public bodies that finance the health system. This stakeholder group has experienced various types of costs due to implementation of the EU Orphan Regulation. Some are directly related to the Orphan Regulation, while others are related to the impact of the EU Orphan Regulation as assessed above e.g. the extra health care expenses.

The direct costs are:

- **EMA/COMP costs:** the additional costs resulting from the tasks that EMA executes in relation to the Orphan Regulation, as well as the cost borne by the EEA Member States and other organisations in relation to the meetings of the various committees discussing applications for orphan designations and marketing authorisations. Annual costs for EMA and national governments have been assessed based on the approximate number of staff (in full time equivalents) involved in the various activities relating to the EU Orphan Regulation.
- **Research subsidies:** the EU and various national governments have provided subsidies for research to stimulate the development of orphan medicines. These subsidies are seen as fully additional costs – these costs are assumed not to have been made without the EU Orphan Regulation. This may be an overstatement, as some of these public R&D programmes would have been supporting research on rare diseases even if the EU Orphan Regulation had not been implemented. However, with the very limited information that is available, we have not been able to assess the extent to which these additional R&D expenditures would have been incurred in a situation without the EU Orphan Regulation.
- **Fee waiver and protocol assistance:** this is an integral part of the support provided by the EMA in line with its mandate to implement the EU Orphan Regulation; the costs of this assistance, which are incurred by the EMA, are fully financed by the EU.

The more indirect costs relate to the public share in the expenditures on health care system, as shown in section F5.3.2 above.

Table 40 shows the estimated additional costs for governments due to the Orphan Regulation. The net costs have been estimated at € 24 billion. The results are sensitive to the assumption regarding the additional development of orphan medicines and the faster/wider availability of orphan medicines. In case lower or higher estimates are used for these variables (same scenario as described for industry in section F5.3.1), total additional costs range between € 22 and € 27 billion.

Table 40 Costs and Benefits due to the Orphan Regulation for governments, 2000-2017 (discounted value 2018, prices 2018, € billions)

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

F5.3.4 Costs and benefits for Patients (and others)

The fourth stakeholder group concerns the patients suffering from rare diseases. It potentially also includes the circle of persons associated with those patients (carers, relatives, etc.) and others in society, but the impact on their costs and benefits could not be assessed – the CUA therefore focusses on health-related costs and benefits for patients.

The various cost and benefits items for this group relate to:

- **Private payments for health care costs:** as indicated above it has been assessed that almost all additional health care costs relating to treatment with orphan medicines are financed from public sources. The private contribution by patients is assessed at 3% of additional health care costs;
- **Health benefits** due to treatment with orphan medicines: these have been assessed on the basis of the extra availability (use) of orphan medicines in the EU due to the EU Orphan Regulation. The benefits have been assessed by applying the ICER (€54,000 to €110,000) to the additional sales volume (€ 23.7b).
- The **non-health costs** of a rare disease. As explained the impact of additional use of orphan medicines on non-health costs of rare diseases could not be assessed.

Based on the extra health care costs estimated and the midpoint of the above ICER range, the additional health impact due to the Regulation is estimated to be 210,000-to 440,000 QALYs. This results in the following overview of costs and health benefits for the stakeholder group patients:

Table 41 Costs and Benefits due to the Orphan Regulation for patients, 2000-2017 (discounted value in 2018; prices 2018, € billion)

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

a: NDA: not sufficient data available to assess this effect

For this stakeholder group as well, the results are sensitive to the impact of the EU Orphan Regulation in terms of generating new orphan medicines and the faster and wider availability of orphan medicines. The results are, however, most sensitive to the ICER applied, as can be seen from the range for health benefits shown in Table 41 above.

F5.4 Costs and benefits to society

This section presents an overview of total costs and (health) benefits to society resulting from the EU Orphan Regulation over the years 2000-2017. As with the individual stakeholder presentations, the overviews uses constant prices 2018, while discounting has been applied.

Table 42 Costs and benefits associated with the Orphan Regulation 2000-2017 (discounted value 2018, prices 2018, € billion)

Effect	Patients	Industry	Governments	TOTAL
COSTS				
Aid for research			-/- €1.1b	-/- €1.1b
Fee waiver, protocol assistance		+ €0.2b	-/- €0.2b	€0b
Administration			-/- €0.02b	-/- €0.02b
R&D costs new orphan medicines		-/- €11.0b		-/-€ 11.0b
Extra costs manufacturing, marketing, distribution orphan medicine, "normal profit"		-/- €13.4b		-/- €13.4b
Additional impact on health costs	NDA		NDA	NDA
Extra health care cost financing	-/- €0.7b		-/- €23.0b	-/- €23.7b
BENEFITS				
Extra sales revenues		€23.7b		€23.7b
Change in non-health costs of disease	NDA		NDA	NDA
NET BENEFITS	-/- €0.7b	-/- €0.5b	-/- €24.3b	-/- €25.5b
ICER	€ 54,000-€ 110,000 per QALY			
Health impact	210,000-440,000 QALYs			
Net societal cost per QALY	€58,000-€118,000			

a: NDA: not sufficient data available to assess this effect

This overview shows that the extra health care expenses by governments and patients as a result of the EU Orphan Regulation in 2000-2017 are estimated at nearly €24 billion. Total costs to society have been estimated to be slightly higher, at €25.5 billion. The extra health impact is estimated at 0.2- 0.4 million Quality Adjusted Life Years of patients suffering from rare diseases.

It should be emphasised that some important elements of societal costs and benefits could not be assessed with reasonable levels of robustness. These are indicated with "NDA".

F5.5 Sensitivity analysis

The above calculations use the most likely estimates, representing averages for the whole group of orphan medicines. As noted, there are uncertainty ranges around these averages. Applying the minimum and maximum levels would give different levels of societal costs and benefits.

The most important driver of this result is the ICER applied, as this ratio translates the extra costs for the health care system to the health impact. The impact on the result is substantial because the total costs to society as calculated above are close to the additional health care costs. The sensitivity to the ICER is already shown in the tables above.

Other inputs that are important for the outcome of the analysis relate to the impact of the Regulation and the discount rate used. The table below shows the result in terms of societal cost per QALY in case various alternative assumptions are applied. Apart from the ICER value, the estimate of societal costs per QALY is most sensitive for the assumption regarding the relative importance of sales in the EU market for the (newly developed) orphan medicines.

Table 43 Societal cost per QALY gained as a result of the Orphan Regulation in various scenarios (in Euro)

Sensitivity analyses	Societal cost per QALY	
Baseline analysis	€58,000 – €118,000	
Baseline analysis, monopoly rent only for medicines with generic competition (44% of the total group)	€52,000 – €106,000	
Baseline analysis, extra spread as a result of Regulation 5% (instead of 2.7%)	€57,000- €116,000	
Baseline and Lower (479 m) / higher (725 m) R&D costs per orphan medicine	€53,000 - €107,000	€63,000 - - €128,000
Baseline and Lower (18) / higher (24) number of orphan medicines developed extra	€55,000- - €112,000	€61,000- €124,000
Baseline and turnover in EU market as share in worldwide turnover lower (21%) / higher (100%)	€42,000 - - €85,000	€75,000 - €152,000
Baseline and lower (1%) / higher discount rate (5%)	€56,000 - - €114,000	€60,000 - - €122,000

The results in this table relate to the period 2000-2017. However, as the orphan medicines are still available (and new orphan medicines have been registered since December 2017) the various costs and benefits will continue in the future. Even if no additional orphan medicines were to receive marketing authorisation over the next years, the costs and benefits for the industry, health system, government and patients would continue to be incurred because of the use of previously developed orphan medicines.

Non quantifiable factors

The above quantitative analysis only takes into account those factors for which a quantitative assessment could be made. Important to note is that various other factors are also of relevance, even though their quantitative impact could not be established. The following table describes the most important of those factors for which no credible quantification could be made, including a qualitative assessment of the impact on the above presented outcome.

Table 44 Assumptions and non-quantified factors and their impact on the CUA

Factor / assumption	Impact on outcome of CUA
No supply side efficiency gains for industry taken into account	The assessment of both the development of new orphan medicines and production costs, does not take into account that larger industries may realise efficiency gains due to scale, nor efficiency gains due to technological advancement (e.g. improvement of genome technology). This may lead to overestimation of the costs, as well as an overestimation of the impact of the Regulation in terms of development of new orphan medicines.
Survivor bias in orphan-like comparison group	The effect of the EU Orphan Regulation on the time to market and geographic spread may be estimated conservatively. The health impact may have been underestimated accordingly.
Additional protection from market exclusivity compared to patent	By only quantifying the effect of a longer protection period (i.e. 3.4 years), the economic value of the market reward may have been underestimated, as the additional protection of the market exclusivity from similar products is not taken into account. This implies that the benefit for industry may have been underestimated, as well as the societal cost per QALY.
Well established use not included in modelling	The analysis assumes that all newly developed orphan medicines concern medicines which were not available previously. In case of marketing authorisation on the basis of well-established use the costs and health impacts may be overstated.

Factor / assumption	Impact on outcome of CUA
The analysis is limited to 2000-2017	The medicines that are developed due to the Regulation will continue to generate health impacts. A longer time period may show higher revenues for industry, but also higher additional health care costs and a higher health impact. As the development costs are fully taken, but health impacts continue after 2017, total societal costs per QALY could be overestimated.
Impact on health care costs restricted to use of orphan medicines	The effect on health costs may be smaller or larger, depending on the total costs of treatment and the saved costs of comparator treatment. This implies uncertainty on the additional health costs and the additional health impact
Indirect economic benefits are not quantified	There may be more benefits to society than shown above, but also more costs to society. The net effect of this on societal cost per QALY is not clear.
Health care expenses and health impacts calculated are realised over a longer period than the period of analysis	The health care expenses and the health care impact included in the HTA reports represent the long term impact of use of orphan medicines. In case orphan medicines prolong life substantially the expenses and impacts may extend be well beyond the timeframe of the analysis. As both costs and impacts are discounted, this may have an impact on the result of the analysis, in particular when costs are made upfront and health impacts cover a long period, well beyond the period used in the analysis. Due to this there may be an overestimation of the health impact for some of the orphan medicines.

Appendix G Aid for research Member States

Member State	Measures / instruments
Austria	<ul style="list-style-type: none"> • Austrian National Plan for Rare Diseases (NAP.se, 2011-2018) including a (one-off) €5m subsidy for research of rare diseases; • Rare disease research is funded through the general programme of the Austrian Science Fund.
Belgium	<ul style="list-style-type: none"> • The Belgian National Plan for Rare Diseases (2013-undefined) is funded to the amount of €15m per year; • Rare disease research supportive programmes are the Fund for Scientific Research the French-speaking community of Belgium and Fund for Scientific Medical Research; • Bilateral agreement with the Netherlands on jointly assessing the potential added value of orphan drugs and negotiating with pharmaceutical companies; • Regulatory fee waivers (for clinical trials).
Bulgaria	<ul style="list-style-type: none"> • The National Plan for Rare Diseases is expired (2009-2013) and had a total budget of €11.3m (€2.3m per year). No new plan has started; • There is a rare disease programme: the Institute for Rare Diseases; • Unauthorised medicinal products can be administered by a committee; • Public funding for orphan drugs (ministry budget & national health insurance fund); • Fund (2004) providing organisational and financial support for treatment of children abroad (treatment cannot be given in Bulgaria).
Croatia	<ul style="list-style-type: none"> • The National Plan for Rare Diseases (2015-2020) has according to EUROPAS a 'modest budget'; • A rare disease research programme is outlined in the national plan; • Dedicated fund for (very) expensive medicines.
Cyprus	<ul style="list-style-type: none"> • National Strategic Plan for Rare Diseases (2012-Unknown); • Rare disease research programmes are part of the general health budget; • Public funding is available through the Cyprus Research Promotion Foundation (not dedicated to orphan medicines); • Named patient supply of medicinal products for pre-authorisation access.
Czech Republic	<ul style="list-style-type: none"> • The Czech Republic had several plans: National Strategy for Rare Diseases (2010-2020), National Action Plan for Rare Diseases (2012-2017), a third was under preparation; • The pricing and reimbursement of orphan medicines is governed by the Act on Public Health Insurance; • Regulatory fee waivers.
Denmark	<ul style="list-style-type: none"> • National Strategy for Rare Diseases (2014-2019). The 2014 National Strategy for Denmark on Rare Diseases contains 97 recommendations, including on how to ensure access to necessary orphan medicines in Denmark;

Member State	Measures / instruments
	<ul style="list-style-type: none"> • Rare disease research programmes are part of the general health budget; • Pre-authorisation access to orphan medicines through compassionate use ('patient supply'); • Free experimental (named patient) treatment in highly specialised hospitals under certain circumstances; • All medicinal products with orphan designation are reserved for hospitals. Access to hospital and GP healthcare is free of charge for Danish citizens; • (Regulatory) fee waivers.
Estonia	<ul style="list-style-type: none"> • Estonian National Health Plan (2009-2020). There are rare disease research programmes: Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products, Eesti Teadusfond (this last fund is worth €40k – €65k over four years, but not specifically for rare disease research); • Applications for the reimbursement of orphan medicines can be submitted with appendices in English (not translated into Estonian, like applications for regular medicines); • Exception to the rule that the pharmaco-economical evaluation has to be tailored to conditions in Estonia.
Finland	<ul style="list-style-type: none"> • The National Plan for Rare Diseases (2014-2017) gets the minimal funding for an expert group, amount unclear; • In addition, The Academy of Finland supports (genarl) health sector research with €40m annually; The ministry of Social Affairs and Health has in collaboration with other stakeholders earmarked €17m for the establishment of the National Genome Centre and the Comprehensive Cancer Centre Finland, and for the harmonisation of biobank activities in 2017–2019.
France	<ul style="list-style-type: none"> • The first and second French National Plan for Rare Diseases (2005-2013). The first got €100m funding, the second €180m (i.e. on average €31m per year). A third plan has been announced, budget is still unknown; • The French Foundation for Rare Diseases supports research. Basic research for rare diseases was granted €113m between 2005 and 2011, representing 327 projects over these 7 years. Clinical research received €9m (36 projects) in 2010, €8.3m (23 projects) in 2011 and €8.5m (21 projects) in 2012; • The Ministry of Higher Education and Research funds the RaDiCo (Rare Diseases Cohorts) project, running from 2011 – 2020 for a total of €10m; • OMP developers are exempt from several taxes; • Free scientific advice from ANSM (also for non-orphan medicines); • Patients can be treated before marketing authorisation via compassionate use programmes; • Framework agreement between CEPS (the French pricing committee) and industrial representatives sets out specific pricing procedures for orphan medicines.

Member State	Measures / instruments
Germany	<ul style="list-style-type: none"> • The National Plan of Action for People with Rare Diseases (2013-Unknown); • A specific programme was the Federal Ministry for Education and Research (BMBF) program. This had the values of €31m in 2003, €24m in 2007, €6m in 2010, €23m in 2012, €20m in 2013 and €20m for 2015/2016; • The BMBF is expected to fund 11 research consortia from 2019 to 2022 with a total of around €25m. The BMBF also participates in the ERA-Net on Rare Diseases. Since 2007, nine joint calls for funding have been implemented in which the BMBF has contributed €27m. The BMBF also provided thematic funding, which has totalled more than €15m per year in recent years (source: Technopolis survey); • The participation in E-Rare was worth €13m in total in 2007, 2009, 2011 and 2012. It was worth €2.8m in 2013, €2.7m in 2014, €5.4m in 2016 and €5.3m in 2017; • Fee waivers; • Compassionate use programmes (no marketing authorisation required in certain circumstances); • Once authorised at European level, all orphan medicines are fully reimbursed by the statutory health insurance (GKV); • Orphan medicines with an annual turnover below €50m are exempt from the cost/benefit analysis, as the benefit is taken for granted.
Greece	<ul style="list-style-type: none"> • The Greece National Plan is expired (2008-2012); • Rare disease research is funded through the general budget for the general Secretariat for Research and Technology; • Greece participated in E-Rare for €462k; • Compassionate use programme; • Special pricing conditions (Orphan medicines are priced on the basis of prices in at least two other Member States); • Special reimbursement conditions in the post authorisation phase; • No co-payment in the majority of cases; • Development of a national rare diseases plan.
Hungary	<ul style="list-style-type: none"> • In 2016, the National Plan for rare diseases (2014-2020) was not yet approved; • Hungary participates in E-Rare, with a budget of €150k yearly; • (Regulatory) fee waiver (under consideration); • Programmes to simplify access to orphan medicines; • Service providing public and healthcare professionals with information on the availability of medicinal products for rare diseases.
Ireland	<ul style="list-style-type: none"> • The National Plan for Rare Diseases (2014-2018) supports research on rare diseases; • There is a National Clinical Programme for Rare Diseases which got €850k from the Ministry of Health budget for charity led investments; • Investments into research were in total €6.9m as of 2016;

Member State	Measures / instruments
	<ul style="list-style-type: none"> • (Regulatory) fee waivers; • Access to unauthorised medicines through clinical trial participation.
Italy	<ul style="list-style-type: none"> • National Plan for Rare Diseases (2013-2016); • There are specific programmes: Ministry of Health programme, Iss, Italian Drug Agency (AIFA), Ministry of Education, university, Research National Council, Telethon foundation. The Ministry of Health invested €30m in 2008, €20m in 2009 and €5m in 2010 and beyond. AIFA invests €45m per year. The Telethon foundation invested almost €100m invested in 2011-2014; • (Regulatory) fee waivers; • The E-Rare budget was €1m; • Access to treatment for patients suffering from a rare disease is guaranteed through various legislative instruments, in particular the compassionate use programme; • Dedicated fund for unauthorised orphan drugs awaiting approval; • Orphan medicines are made available, though not reimbursed, within 60 days of the publication of the relevant Commission decision in the EU Official Journal; • An economic protection mechanism for the holders of marketing authorisations for orphan medicines.
Latvia	<ul style="list-style-type: none"> • Latvian National Plan (2013-2015, 2017-Undefined is under preparation); • Research is funded through the general health budget; • Measures for the distribution of unauthorised medicines through a compassionate use programme; • Some orphan medicines (notably for children) are reimbursed.
Lithuania	<ul style="list-style-type: none"> • National Plan for Rare Diseases (2012-2017), no specific budget; • There were several projects regarding rare disease research.
Malta	<ul style="list-style-type: none"> • Malta has no national plan and no rare disease research programmes; • (Regulatory) fee waivers; • Compassionate use programmes and named patient supply; • 'Treatment abroad' scheme for patients requiring tertiary-level healthcare, including treatment for rare conditions or complications; • Access treatment without waiting for the specific disease to be included in the Social Security Act.
The Netherlands	<ul style="list-style-type: none"> • The Dutch National Plan for Rare Diseases (ZonMW) received a total budget of €13.4m as of 2011; • ZonMW got a budget allocated for specific tasks of €280k per year for the period 2012-2015; • The Ministry of Health, Welfare and Sports supports eight University Medical Centres with each €80 m per year. 20% of this budget is allocated for research and innovation (but this is not necessarily dedicated to research of rare diseases);

Member State	Measures / instruments
	<ul style="list-style-type: none"> • The Ministry of Health, Welfare and Sports also funds FBG, the Biotechnology and Genetics Forum, with an amount of €125.000 annually and the Erfocentrum with €250.000 annually; • (Regulatory) fee waivers; • Tax reductions for R&D by high-tech start-ups; • Innovative research incentives scheme based on a bottom-up approach and several subsidy schemes;
Poland	<ul style="list-style-type: none"> • The National Plan for Rare Diseases (2014-Unknown), is expected to have a budget of €33.2m per year; • Under this programme fall several rare disease research projects; • Rare disease research is part of the general health budget.
Portugal	<ul style="list-style-type: none"> • The National Strategy for Rare Diseases (2008-2015) is expired; • There is a rare disease research programme: The Integrated Strategy for Rare Diseases (2015 - 2020); • A special-use authorisation procedure provides access to certain orphan medicines; • Most orphan drugs in Portugal are dispensed at hospitals without any co-payment; • Centres of expertise for lysosomal disorders; • Coordinating committee responsible for monitoring access to dedicated orphan medicines; • Specific card for the identification of people with rare diseases.
Romania	<ul style="list-style-type: none"> • National Plan for Rare Diseases (2014-2020), with a budget of €1m per year; • An order of the Minister for Health on approval of the terms for the granting of authorisations for compassionate use and an order on addressing special needs (for a named patient or a group of patients) provided for several means of access to orphan medicines; • A March 2015 amendment of the Minister for Health's order on the approval of inclusion criteria facilitates the (conditional/unconditional) inclusion of orphan medicines in the list.
Slovakia	<ul style="list-style-type: none"> • National Plan for Rare Disease Patients (2016-2020), had a budget of €240k in 2016 and 2017; • Medicinal products to treat diseases with prevalence of less than 1:100 000 can be reimbursed from the public health insurance system; • The costs can exceed the limit for other medicinal products; • Re-evaluation of reimbursement after 2 years.
Slovenia	<ul style="list-style-type: none"> • The National Plan for Rare Diseases (2012-2020) gets funded through the Contact Point for Rare Diseases and the Platform for the National Registry for Rare Diseases; • The rare disease research programme is the Analysis and Development in the field of rare Diseases in Slovenia; • (Regulatory) fee waivers;

Member State	Measures / instruments
	<ul style="list-style-type: none"> Compassionate use programme.
Spain	<ul style="list-style-type: none"> Strategy for Rare Diseases (2013-Unknown); There is a rare disease research programme: Strategic Action in Health (2013-2016); Several measures to support R&D on orphan medicines; Several measures to support the availability of orphan medicines to patients; The public Carlos III Health Institute (ISCIII) funds various projects. From 2001 – 2003 it funded the Fund for Health Research with a total of €20m. In 2007 it funded projects for a total of €6.2m, in 2008 €8m, in 2009 €12m, in 2010 €5.8m. The institute financed the Spanish Rare Diseases Registries Research Network with €2.4m in the period 2011 – 2014; ISCIII created CAIBER, the Spanish Clinical Trials Platform, which has a budget of €10m per year. ISCIII also created RetBiOH, a network of biobanks, which has a budget of €6m per year.
Sweden	<ul style="list-style-type: none"> The Swedish strategy did not get adopted; Incentives for academics, including fee waivers for clinical trial applications and free scientific advice for potential or designated orphan medicines; Compassionate use programmes and named-patient prescriptions.
UK	<ul style="list-style-type: none"> The UK Strategy for Rare Diseases (2013-Undefined); The National Institute for Health Research had £800m available over a period of five years for general health research. Of this budget, £50m per year is available for Genomics England; The Medical Research Council made €74.2m available over a period of five years (2012 - 2016) for research on inherited disorders, including rare diseases; Free scientific advice (also for regular medicines); Early Access to Medicines Scheme (EAMS).