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signed by Mr Jordi AYET PUIGARNAU, Director

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To: Mr Jeppe TRANHOLM-MIKKELSEN, Secretary-General of the Council
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evaluation of Regulation (EC) No 1901/2006 of the European
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European Parliament and of the Council of 16 December 1999 on
orphan medicinal products

Delegations will find attached document SWD(2020) 163 final, PART 3/6.

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PART 3/6

COMMISSION STAFF WORKING DOCUMENT

EVALUATION

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

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

ANNEX 3: METHODS AND ANALYTICAL MODELS

Orphans

External support study

The support study was conducted by Technopolis Group and Ecorys for the European Commission. The 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.

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. For more detailed information on the stakeholder and open public consultation, please refer to Annex 2.

The primary data analysis was supported by several secondary data analysis activities.

Literature review

To support the various activities of the 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. The screening was based on predetermined selection criteria (based on the relevance of the content, i.e. whether there was information that would help answer an evaluation question). 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.

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 the Orphan Regulation. For the first, no restrictions were posed on geography, intervention or impact area.

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.

Portfolio analysis

The portfolio analysis is based on analysis of the data received from the Agency and IQVIA. This comprehensive set of data was cleaned from data entry errors, restructured, according to the orphan designation, and linked to ensure that the contractor was able to run the proposed analyses.

Classification of sponsor types

Sponsors were classified to compare the composition of different types at the time of orphan designation to marketing authorisation. Overall, the following classifications and definitions were used.

Table A.3: 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 Agency's 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.

Classification by geographical origin of sponsor

An online hand search was conducted for all sponsors to establish where their corporate headquarters are located.

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.

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 listed as ‘protein based therapies’ on [http://www/drugbank.ca](http://www.drugbank.ca), were all classified as **biological**.

Those included fusion products that were produced at least in part through a biological process, as well as cell extracts and cell cultures. 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 Agency first officially introduced the ATMP classification. All other products were classified as **small molecules**.

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, the contractor calculated the potential patient population size in Europe. They took into account 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, the contractor 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. It 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.

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, the contractor used data from MPA Business Services, which was linked to the data of the Agency. 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. The contractor excluded patents on formulation and/or process. As a reference for protection in the EU, it selected four countries to check if

they had any protections on the active substance. These four countries were Germany, France, UK and Italy (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).

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. Subsequently, a regular division was done of the sum of the prevalence by the frequency of designations/OMPs.

Economic analysis

The IQVIA-database containing information on medicine sales was an important data source for the support 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.

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 (contractor) had access to revenue and volume data for the period 2008 (first quarter) to 2017 (third quarter) for the geographical area ‘Europe’.

For the analysis, information on the following three subsets of medicines was abstracted from the database:

- EU orphan medicinal products and their generics
- Orphan-like products and their generics
- Non-orphan products

1.1. EU orphan medicinal products

The IQVIA database did not provide an identifier for orphan medicinal product as such. Therefore, orphan medicines that received MA in EU were identified based on the active

substance and the (local and international) product name. A list of medicines with MAs in the EU was obtained from Orphanet Report Series (July 2018)¹ and matched to the list of product names (both local and international) in the IQVIA-database. The list was also cross-checked with the information provided by the Agency. A list was then extracted for the identified matches, based on the International Non-Proprietary Names (INN) together with the way the products are administered. It is further assumed that products, which have the same combination of active substances and way of administration are generic products for this orphan medicine.

1.2. 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 orphan-like medicinal products have ‘orphan’ characteristics, such as (potentially) low sales volume and use in the treatment of somewhat rare diseases.² 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 steps described above for orphan medicines.

1.3. Non-orphan medicines

Non-orphan medicines were identified separately in IQVIA database, after orphan medicines and orphan-like products were filtered from the data, by matching the complete list of IQVIA data with previously made lists (of orphan medicines and orphan-like products). The remaining list was regarded as containing only non-orphan medicines.

1.4. Calculation of the economic value of market exclusivity reward

As part of the study, the economic value of the market exclusivity reward was estimated. Two dimensions were important for this analysis:

¹ Available at https://www.orpha.net/orphacom/cahiers/docs/GB/list_of_orphan_drugs_in_europe.pdf, last accessed in August 2018.

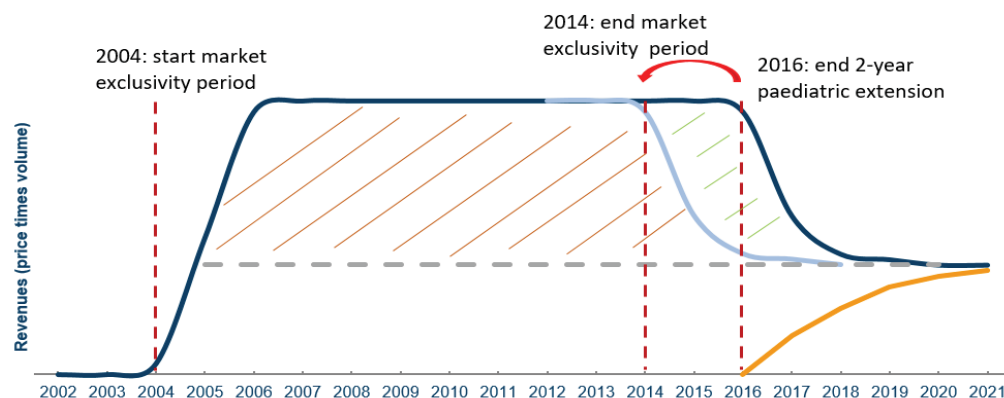
² Under the US Orphan Drug Act a rare disease was defined as one that affects fewer than 200,000 people in the US (approx. 7 in 10,000). This is slightly different from the definition under the EU Orphan Regulation. See also Chapter 2 of the main report.

- i) **The monetary impact of the reward for society as whole:** due to the longer period of market protection (associated with the orphan market exclusivity reward) and the delayed generic entry into the market, society is unable to benefit from increased competition and lower prices for the used medicines.
- ii) **The actual comparator situation:** the situation *without* 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.

A group of 16 orphan medicines was selected for further analysis. This group was 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. 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. 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.

For the purpose of the analysis of the economic value of the market exclusivity, it was assumed that, in the case of a generic entry, the price of branded and generic products was expected to converge, and a new equilibrium price was reached (see Figure B.0).

Figure B.0: Illustration of calculation of the economic value of market exclusivity



Source: Orphan Study (2019)

The new equilibrium price³, 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 for the reference product can be seen as the compensation for R&D costs.⁴

For this analysis, 16 orphan medicines were identified for which the period of market exclusivity had ended and where there were at least two years of IQVIA-data available after the end of the exclusivity period. In 2016, in total nine products were free from patent or regulatory protection and, in theory, susceptible to generic competition. No generic entry was observed in five of these nine cases. One product was still under market exclusivity in the US. Although this does not preclude generic entry in the EU, such generic entry was still not visible.

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 €10 million, only in one case was it below €10 million. For all four products, it was possible to determine a new equilibrium price, based on the price realised by competitors. The economic value of market exclusivity reward for this limited sample of products was on average 30% of total turnover.⁵

1.4.1. 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.

³ 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.

⁴ 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.

⁵ For detailed calculations see Section 2.1. in Annex 3.

A selection of products was made with a patent/SPC expiry date between 01-01-2011 and 09-01-2015; the 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.

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.

The equilibrium price was calculated per market and per quarter, by making the assumption 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

The counterfactual revenues⁶ were calculated by multiplying the standard units per market for generic and branded products with the equilibrium price.

The economic value is calculated per quarter and per market for branded and generic products, by subtracting the counterfactual revenues per market from the actual revenues.

The relative value of the patent is calculated, as a percentage of the revenues, for branded and generic products

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%.

1.4.2. Assessment of societal costs and health impacts

The analysis of societal costs and health impacts of the Orphan Regulation follows the methodology of a cost-benefit analysis (CBA), but is different from a CBA in the sense that the health benefits are not expressed in monetary values, but in terms of quality adjusted life years (QALYs).

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.

⁶ 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 evaluation has, as far as possible, been carried out in accordance with EU CBA guidelines.⁷

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 was based on analyses of the IQVIA-database;
2. Translation of the impact on accessibility 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 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. Analysis concerning the division of health care costs between public and private financing sources.
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)

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. 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.

⁷ 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.

As the econometric analyses necessary to come to a counterfactual situation that satisfies the requirements in the Better Regulation Toolbox were not possible, 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.

➔ **Development of new orphan medicines**

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, marketing and distribution 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 more⁸, 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 A.4: Number of marketing authorisations for orphan and non-orphan medicines in EEA

Year	Orphan	Non-orphan	Year	orphan medicines	Non-orphan
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⁸ 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.”

	medicines	medicines			medicines
2000	0	42	2009	9	108
2001	3	29	2010	4	47
2002	4	35	2011	6	81
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

Source: Agency data

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 the Agency on non-orphan medicines in the same periods.

Table A.5: 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: analysis Agency 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% ($21/110 = 19\%$).⁹

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.

⁹ 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).

The extra protection provided by the market exclusivity reward of the EU Orphan Regulation has been used as the defining factor in this analysis.

Among 105¹⁰ authorised orphan medicines analysed, **74 (70%) were protected by a primary¹¹ 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 exclusivity¹², with an average duration of 3.5 years beyond the market exclusivity.**¹³ For these products, the market exclusivity had no impact on prolonging the period of protection.¹⁴

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

¹⁰ 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.

¹¹ 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.

¹² 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.

¹³ 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.

¹⁴ 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.

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 exclusivity period, **the average additional protection offered by the market exclusivity was calculated at 3.4 years.**¹⁵

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 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 %.¹⁶

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

¹⁵ This estimate is based on the following summation: 31 products with the full 10 years of market exclusivity extending beyond any patent/SPC ($=31 \times 10$), 51 products with market exclusivity fully within the period of patent/SPC protection ($=51 \times 0$), 23 products with an average period of market exclusivity after expiry of patent/SPC of 2.25 years ($=23 \times 2.25$). Divided over all 104 products, this gives an average duration of the market exclusivity beyond the primary patent/SPC of 3.4 years.

¹⁶ 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.

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.¹⁷ 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.

➔ **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 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:

¹⁷ The EU share in the combined population of EU and US is approximately 60% (rounded), while its share in the total pharmaceutical market is roughly 50% (based on sales data for 2014 as published by EFPIA).

- 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 A.6.

Table A.6: 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

Source: analysis IQVIA data

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.

➔ 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 relevant:¹⁸

- The potential size of the markets based on population (the EU28 being approximately 33% larger than EU12);¹⁹

¹⁸ 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.

¹⁹ 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-db0d65ea457f>

- 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 EU12.²⁰

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.

→ Higher sales prices of orphan medicines during the period of the 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 through the market exclusivity reward. For this impact, the result of the economic valuation of the market reward 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 2000-2017.²¹

This assessment implicitly assumes that even though not all orphan medicines experience generic entry, there is still additional value realised due to the market protection, as sponsors set their prices not knowing beforehand whether competition will arise. This was deemed 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,

²⁰ 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.

²¹ The other orphan medicines had not yet reached the 6.56 years of market exclusivity at the end of 2017.

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 analysis²², it was 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).

Step 2: translation of the impact on accessibility of orphan medicines

The next step in the CBA involved 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 under step 1 (establishing the impact) also resulted 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 medicines²³ 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: assessment of the impact of extra use of orphan medicines on health care costs

The higher use and higher prices of orphan medicines that can be attributed to the EU Orphan Regulation have resulted 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 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 the University of York Centre for Reviews and Dissemination and a list of HTA reports supplied by EMA.

²² Included at the end of this Annex 3.

²³ Active orphan medicines are those for which the market exclusivity period had not yet expired and which were not withdrawn.

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** provides an overview of the available information in the identified HTA reports).

Table A.7: 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: elaboration by Ecorys. 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.²⁴ 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 A.8: List of 32 orphan medicines used in the evaluation of costs and health benefits at Regulation level

²⁴ 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
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
Blinicyto	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
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
Holoclax	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
Lartuvo	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

OMP	Source
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
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).

The ‘weighted average ICER’ for the individual years 2008-2016 was €54,000.²⁵ However, this number may be an underestimation, as the group of orphan medicines contains medicines that have multiple indications, including indications for non-rare diseases.²⁶ Given the overall conservative nature of the assessment, the cost-effectiveness of the Orphan Regulation for society can be deemed acceptable when compared to ICER thresholds in use internationally.²⁷

Table A.9: Overview of ICER of Orphan Medicinal Products that received Marketing Authorisation

²⁵ 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 (average) ICER of €110,000 per QALY reflects the higher sales revenues for orphan medicines with a lower ICER.

²⁶ Section 8.2.5. of Orphan study report (2019).

²⁷ See for instance the threshold of 80.000 per QALY in the Netherlands (<https://kce.fgov.be/sites/default/files/atoms/files/d20081027396.pdf>).

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), 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 €54,000.²⁸

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.

²⁸ 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.

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 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 2018²⁹ 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%).³⁰ 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.

²⁹ European Commission, see: <https://ec.europa.eu/eurostat/statistics-explained/pdfscache/37773.pdf>

³⁰ 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.

In addition, in this study's survey of national public authorities, it was 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;
- 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 for this 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 cost-benefit analysis 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.

2. Costs and benefits per stakeholder group

This section of Annex 3 presents the costs and benefits for individual stakeholder groups, based on the results from the six steps described above.

2.1. Industry

The impact of the EU Orphan Regulation has resulted in the following effects for industry:

1. 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; 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 $21 \times € 602 \text{ m} \times 60\% = € 7.6$ 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.**

2. 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 $21 \times \text{€ } 67\text{m} = \text{€ } 1.4$ 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.³¹ Total additional turnover for 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.

3. 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)

³¹ 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.

4. Extra production costs due to extra sales

The extra sales realised by industry means that extra costs have been incurred or manufacturing, distribution and marketing of the medicines. These extra costs have been assessed on the basis of the insights from the analyses presented about the calculation of the economic value of the market exclusivity reward. In this analysis, it was concluded that during the period in which products are protected from competition, a higher prices 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.³² 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).

5. Extra revenues due to higher prices

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).

6. Protocol assistance, fee waiver

³² The analysis about the calculation of the economic value of the market exclusivity 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. A competitive profit margin of 10% was assumed (and added to the cost-benefit analysis as a benefit) of the 'net' turnover (i.e. turnover minus the orphan exclusivity share). Please refer to Annex 4 for the consolidated table cost-benefit for pharmaceutical industry.

The sector has directly benefitted 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 (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 analyses³³ 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 a 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

³³ See also end of this Annex 3.

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 A.10: 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 ³⁴	
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.

2.2. Health care sector

The impact of the EU Orphan Regulation on the health care sector is two-fold.

First, 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.

Second, 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.

³⁴ As explained in Chapter 4.1 (Data gathering, methodology and analysis) Chapter 5.2 (Efficiency), the European Commission did not agree with the conclusion of the cost-benefit analysis for pharmaceutical industry. This cost-benefit has been further refined by adding a competitive profit margin of 10%.

This results in the following costs and benefits due to the EU Orphan Regulation for the health sector.

Table A.11: 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.

2.3. 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.

Table A.12: 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, total additional costs range between € 22 and € 27 billion.

Table A.12: 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

2.4. 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 resulted in the following overview of costs and health benefits for the stakeholder group patients:

Table A.13: 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 above.

2.5. 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 A.14: 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”.

3. 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 A.15: 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 A.16: 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.

Paediatrics

External support study

The study ('Study on the economic impact of the Paediatric Regulation, including its rewards and incentives'³⁵) was conducted by Technopolis Group and Ecorys for the European Commission. The study has drawn from a variety of data sources, including from targeted stakeholder groups using a series of interviews, literature reviews and databases searches. Its

³⁵ https://ec.europa.eu/health/sites/health/files/files/paediatrics/docs/paediatrics_10_years_economic_study.pdf

aim was to provide a review of the economic impacts of the Paediatric Regulation since it entered into force until the end of 2015.

1. Regulatory cost to industry

Cost estimates are based on a consultation of PIP and waiver applicants by means of a survey questionnaire and follow-up interviews. Further details of the survey can be found in Annex A of the economic study. The survey was sent to all PIP/waiver applicants that have made 3 or more PIP or waiver applications and, in addition, participants of the EU Framework Programme projects that submitted a PIP. The request to provide information on specific PIPs was thus sent to 78 companies that submitted an estimated 870 PIP/waiver applications. Note that the total number of PIP/waiver applications requested per company was capped at a maximum of 10 for practical reasons, resulting in a target sample population of 514 applications, representing 40% of the total population of 1,297 applications between 2007-2015.

The cost analysis is based on data collected from 26 organisations which includes 19 companies and 7 Framework Programme participants. Company data is collected with a response rate of 24%, which is considered satisfactory due to the difficulty for companies to retrospectively collect information on specific PIP costs incurred by different teams of staff across the company and due to the confidential nature of such information. The 26 organisations that provided data voluntarily include several EFPIA member companies, one non-profit organization and six small and medium-sized companies (SMEs).

In total, data was collected on 36 waiver applications from 11 organisations (not all organisations submitted a waiver application) and on 85 PIPs from 24 organisations (two organisations only submitted waiver applications). Figure B.1 presents a breakdown of the sample of PIPs according to their stage at the time of data collection. All of the PIPs had completed the initial application phase. Only four of the 85 PIPs in our sample had not yet started the R&D stage. The majority, 50 PIPs, were ongoing, 14 PIPs were discontinued and 17 PIPs had received a final compliance check. As presented in Figure B.2, 11 of the PIPs in the sample correspond to medicinal product marketed in at least one EU member state. This represents a deliberate oversampling of PIPs that have received the final compliance check and/or have been put on the market. The reason for this sampling was to gain information on PIPs that have more complete data on late R&D phases. Cost information was then estimated by analysing data obtained for the sample and using this data to gross up figures to characterise the entire population.

Figure B.1: Distribution of PIPs by stage

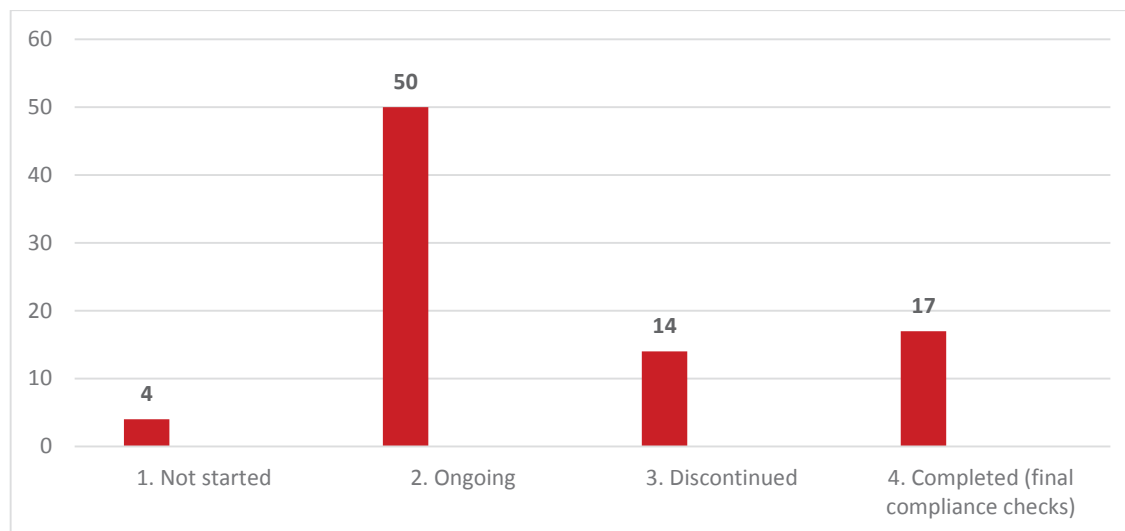
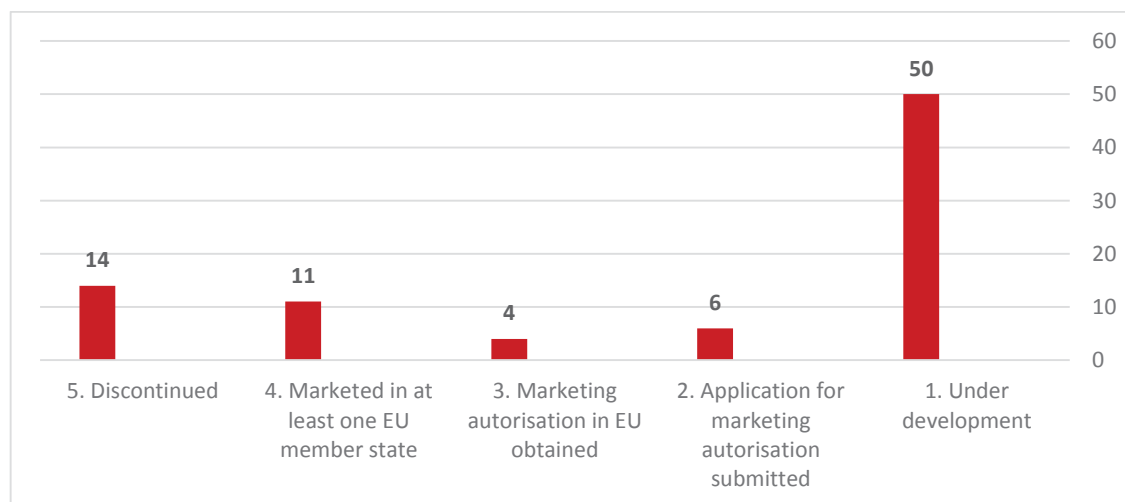


Figure B.2: Distribution of PIPs by paediatric product stage



1.1 The cost of compliance with the Paediatric regulation

The total cost of the Paediatric Regulation incurred to industry is estimated to be €2,106m per year or €16,848m for the years between 2008-2015. This estimate includes €2,103m PIP-related compliance costs and €3.6m costs for waiver applications.

The total cost of the PIPs is estimated based on an average of 107 first PIP decisions per year for the period 2008-2015 (see Table A 16). The estimated average incurred costs per PIP is, based on our sample population, €19,608k which comprises of around €728k for the administrative costs incurred in relation to filing an initial application and for subsequent modifications of a PIP, and €18,879k for the R&D costs (4%:96%). R&D costs may include costs related to:

- In-vitro studies and animal studies
- Development of a paediatric formulation
- Phase II paediatric clinical trials - studies conducted to evaluate the efficacy and safety of the medicine
- Phase III paediatric clinical trials - studies conducted after the efficacy is demonstrated and prior to the approval of the drug
- Other R&D costs

The sample data suggests that an average of 2.9 clinical studies were agreed as part of the PIPs and this implies an average estimated cost per study of €6,831k.

Table A.16: Overview of the total costs of developing and executing PIPs

	Estimated annual costs
Total administrative and R&D costs of PIPs for the industry per year (2008-2015)	€2,103m
Average cost per PIP	€19,608k
Average administrative cost per PIP	€728k
Average R&D cost per PIP	€18,879k

Aggregation is based on an average of 107,3 first PIP decisions in 2008-2015 (858 first PIP decisions in 2008-2015 in total)

The total cost of the waiver application is estimated based on a calculated average number of 50.4 waiver decisions per year for the period 2008-2015. The average cost of the waiver application is €70k, which is about 10% of the estimated average cost of a PIP application. The cost of waiver applications, as reported by companies, comprises of labour costs for literature searches, expert discussions, regulatory and administrative activities. Some waivers were reported to have incurred costs for additional studies (e.g. pre-clinical studies) and some waivers were not accepted in the first instance and there were subsequent costs linked to appeals. All costs reported by companies for waivers were included in the calculations.

1.1.1 Variation in costs by study phase

Figure B.3 presents a breakdown of the total estimated costs to industry by cost category. It is clear that the R&D costs are the largest component of executing a PIP and that there is considerable variation in the estimated cost for each of the R&D phases.

The annual administrative costs linked to PIPs are estimated to be €78m and this comprises of the preparation of the initial application, modification and reporting, and other administrative costs. The preparation of an initial application costs on average €0.4m (Table A.17). Note that this average cost estimate, and the other average cost estimates presented in this section, are often incurred over multiple years. As presented in Table A.17, all PIPs incur some administrative costs, even when the PIP is discontinued. Note that only 55% of the PIPs in our sample was reported to incur additional administrative costs in relation to annual reporting requirements or PIP modifications. In the event that a PIP was discontinued, 29% of the PIPs incur these additional administrative costs.

In-vitro and animal studies are estimated to cost industry €28m each year. 40% of the PIPs include such in-vitro and/or animal studies. On average, the cost of in-vitro and animal studies is €0.8m. If the PIP is discontinued, around 36% of those have already incurred this type of cost before termination.

The total development cost of paediatric formulations is estimated to be €77m per year. 47% of the PIPs incur this type of cost and 29% of the PIPs that are discontinued incur this type of cost. On average, the cost of the development of paediatric formulations, if any cost is incurred, is €1.6m.

Figure B.3: Estimated costs incurred in relation to the Paediatric Regulation broken down to the component, per year, per millions of euro.

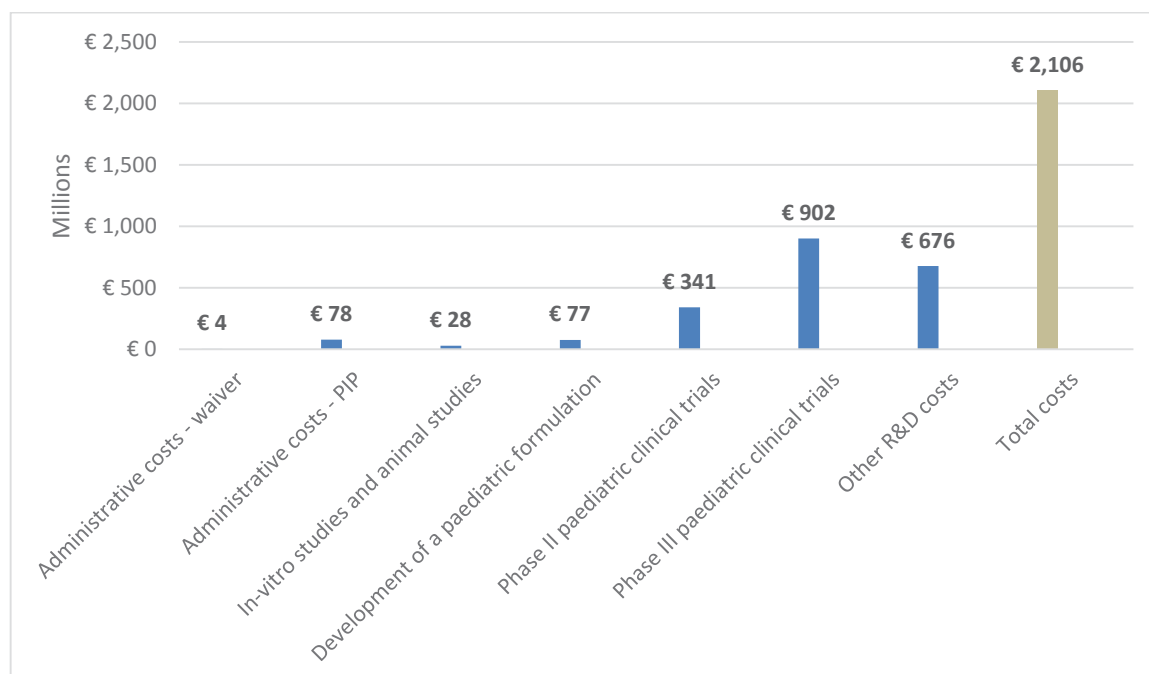


Table A.17 Estimated costs of a PIP broken down by stages, in millions of euro

	Average	Median	Standard deviation	N of PIPs incurring cost	N of PIPs incurring cost if PIP is discontinued
Preparation of the initial PIP application	€0.4	€0.1	0.7	100%	100%
Annual reporting and further PIP modifications	€0.1	<€0.1	0.3	55%	29%
Other administrative costs	€0.2	-	0.5	42%	21%
In-vitro studies and animal studies	€0.8	€0.5	0.9	40%	36%
Development of a paediatric formulation	€1.6	€0.9	1.7	47%	29%
Phase II paediatric clinical trials	€7.3	€1.7	14.3	48%	21%
Phase III paediatric clinical trials	€15.7	€1.5	22.4	72%	36%
Other R&D costs	€14.4	€1.2	22.1	44%	21%

The combined annual cost of phase II and phase III clinical trials to industry is €1,243m: €341m for phase II clinical trials and €902m for phase III clinical trials. Note again that not all PIPs include costs for a given PIP category (or stage). As indicated in Table 3, only 48% of the PIPs have incurred or are expected to incur phase II R&D trial costs and 72% have incurred or are expected to incur phase III R&D trial costs. In some cases, there may be no clear distinction between phase II and phase III costs and some survey respondents have included costs under either phase II or phase III. However, for 38% of the PIPs, data on both phase II and phase III costs is provided. On average, cost for a phase II paediatric trial is €7.3m (median €1.7m) and average cost for a phase III paediatric trial amount to €15.7m (median €1.5m). The standard deviation of the larger cost estimates, as that for phase III paediatric clinical trials, is substantially higher – indicating that there is a high variation between costs incurred and, as expected, some of the more extreme values include very high cost estimates. As described in the next section, there are a number of factors that drive the cost of a PIP stage.

An additional estimated €676m is incurred by industry each year in relation to ‘other’ types of R&D costs. 44% of the PIPs for which we have collected cost data included such ‘other’ costs. On average, the other types of cost amount to €14.4m (median €1.2m). We are not able to fully separate the lower cost elements from the higher cost elements. However, the cost data that falls below the median [with range of approximately €7k-€1,000k] are in relation to observational studies, the preparation of study outlines, medical writing for clinical plan

including data and database management, coordination activities and transaction costs, extrapolation studies and literature study to support extrapolation, other cross-functional paediatric project costs, pharmacokinetics and pharmacodynamics (PK/PD) studies, and bioavailability, modelling. Cost data that is above the median [with range of approximately €1m-€74m] are related to sponsor management costs, pharmacokinetics and pharmacodynamics (PK/PD) studies, pharmacogenomics (PGx) analysis, bioavailability, modelling and simulation studies, and costs related to supporting phase II and III trials.

1.1.2 Attrition

It should be noted that a considerable proportion of PIPs are discontinued and this represents costs incurred by the industry for activities that will not bring any potential reward or revenue to the company. Moreover, discontinued PIPs also place undue burden on paediatric patients involved in associated clinical trials. According to a study of PIPs in the EMA database between 2007-2010, 21% of agreed PIPs were subsequently abandoned because of discontinuation of the adult development programme for the product.³

The total estimated administrative and R&D costs of PIPs that are already discontinued (16% of the PIPs in our sample) amounts to €144m per year, 7% of total estimated costs. This is likely to be an underestimation of the total cost incurred in relation to discontinued PIPs because several of the PIPs that have been labelled as ‘ongoing’ may be discontinued at a later stage in the execution of the PIP.

Any costs associated with waiver applications, albeit much smaller, can likewise be considered as sunk costs to industry – incurred in compliance with the Paediatric Regulation.

1.1.3 Data limitations

In order to produce a cost estimate for the industry, organisations were asked to include only the fraction of their costs that was specifically related to the PIP and to exclude costs related to adult drug development from that of paediatric drug development. Many of the clinical trials however are mixed trials and organisations may have had difficulty to completely separate out costs (even though no such difficulty was reported to the study team). This means that all costs reported are considered ‘incurred’ to comply with the Paediatric 22

Regulation. Without the Paediatric Regulation, costs would not have been incurred unless an organisation would have voluntarily committed to invest in medicine development for children.

Note that incurred costs presented in this study remain cost estimates based on self-reporting by organisations that voluntarily engaged with the study and provided cost data input. These

estimates were provided as best point estimates, however, some of these costs may be overestimations or underestimations. Based on an analysis of industries' practice of pricing drugs, e.g. for (US) Medicare recipients, Angell argues that pharmaceutical companies tend to overestimate (R&D) costs.

As discussed in the next section, there are a large number of potential cost drivers, however, our survey questionnaire was not able to capture all potentially relevant cost components, and further, data supplied by organisations does not allow for a uniform coverage of all dimensions, allowing a robust analysis of every dimension. Despite these limitations, we have been able to extrapolate total cost incurred by industry using the PIP as the unit of reference (and with data obtained on both completed and incomplete phases). Nevertheless, our cost estimates remain subject to possible overestimation or underestimation, e.g. if sample data is not fully representative. In particular, our average and median cost estimates for the 'other cost' category is based on reported incurred costs, sometimes in relation to an ongoing PIP. As a result, there is potential for underestimation in this category.

The cost estimate reflects the costs industry incurred during the years 2008-2015. The cost estimate may not be an accurate reflection of costs that industry will incur in the future as a result of the Paediatric Regulation. During the years 2008-2015, on average, there were 107 decisions on initial PIP applications. Note that since 2012 onwards, the number of initial PIP decisions is stabilising at around 90 per year. This means that projected annual cost to industry, based on the current estimations, is 84% of the cost figures presented above. Similarly, there is a decreasing trend in the number of modifications per PIP and this will reduce somewhat the administrative costs of the PIP (EMA 10-year report). Likewise, organisational learning (both for industry and EMA) may contribute to more efficient/less costly PIP procedures over time.

Other cost items which represent significant costs to industry, related to providing medicine to children, but were out of scope for the current study to assess the compliance cost to industry of evaluating and developing paediatric medicine are the following:

- Cost of long-term safety and efficacy monitoring after marketing authorisation.
- Legal costs of SPC extension (reward) after a positive compliance check.
- Obtaining marketing authorisation for the paediatric medicine.
- Marketing costs of authorised paediatric medicine.
- Manufacturing and distribution costs of authorised paediatric medicine.

1.2 *Costs drivers*

Number of modifications to the PIP

Olski et al. (2011)³⁶ investigated the modifications proposed by the Paediatric Committee (PDCO) of the European Medicines Agency to the PIP applications submitted by companies from 2007 to 2009. Of the 257 PIP applications that had been submitted at the time, the PDCO requested major modifications to 38%. These requests included the development of age-appropriate formulations (11%), expansion of the scope of clinical programmes (6%), addition of a phase II/III study (17%) and the inclusion of additional age groups (13%), generally younger ones.

It is possible that engaging with the Scientific Advice Working Party (SAWP) to request free scientific advice may decrease future PIP costs. Based on our survey results, for 8% of PIPs (7 of 85) scientific advice was thought to have decreased the overall PIP costs – reduction in studies that had been initially planned or benefit of clearer development plan. However, for 7% of PIPs (6 of 85) scientific advice was thought to have increased overall PIP costs – since additional studies were suggested. Other PIPs in our sample were seen not to have benefitted from scientific advice, possibly because no scientific advice was sought. According to EMA’s 10-year report, there has been an increase in scientific advice sought by companies.

Nevertheless, even if a PIP has been agreed, a PIP applicant may request modifications of the PIP at a later stage, eg to reduce sample size of paediatric subjects in the clinical trial.³⁷ Survey respondents reported that the number of modifications to the PIP was seen as a burden and often delayed the execution of the PIP significantly (and possibly also the launch of the associated adult drug) and thus the burden and costs associated can extend beyond the administrative costs involved with requesting a modification. Despite these considerations, many PIPs have been modified once or more, however, according to EMA’s 10-year report, the number of modifications is decreasing over time, possibly as a result of organisations’ learning curve.

Number of clinical studies

The number of clinical studies that are part of a PIP differ considerably across the PIPs sampled. Based on the survey data, the average number of clinical studies that are agreed upon is 2.9. This is slightly higher than the average number of exclusively paediatric trials

³⁶ Olski, T.M. et al., 2011. Three years of paediatric regulation in the European Union. *European Journal of Clinical Pharmacology*, 67(3), pp.245–252.

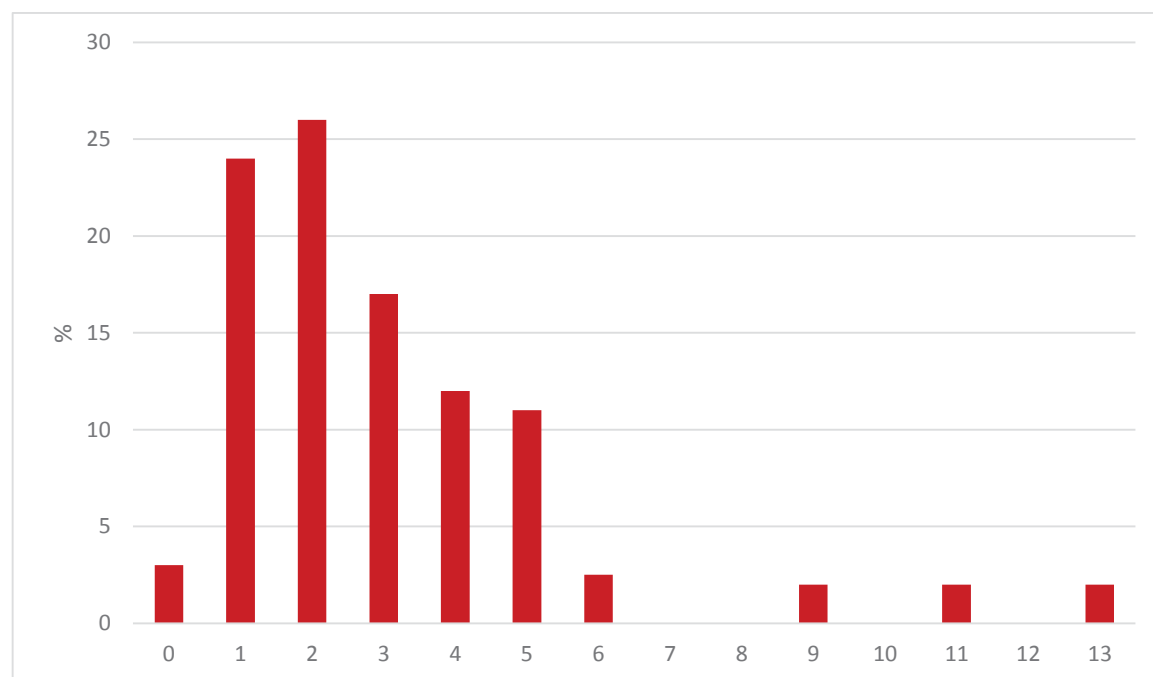
³⁷ Article 22 of the Regulation states: “If, following the decision agreeing the paediatric investigation plan, the applicant encounters such difficulties with its implementation as to render the plan unworkable or no longer appropriate, the applicant may propose changes or request a deferral or a waiver, based on detailed grounds, to the Paediatric Committee.”

per PIP which is 2.4 (Draft 10-year report, EMA/EudraCT). However, only around 18% of the PIPs in our sample involved 3 clinical studies. Just over half of the PIPs involved only one or two clinical studies. Two of the PIPs in the sample did not involve a clinical study (only e.g. a literature review). The highest number of clinical studies that was reported as part of a PIP is 13 (see Figure B.4).

Note that there is considerable variation in cost between the different R&D stages, ie phase II and phase III are considerably more expensive than in-vitro/animal studies and the development of a paediatric formulation. However, in our sample, not all PIPs incurred costs (or expecting to incur costs) in all categories/stages. It is clear that those PIPs that will involve multiple stages, and include phase II and phase III trials, will be more expensive.

In relation to the number of clinical studies that are part of a PIP, there are also important differences in the number of sites and the locations of sites and associated wage differentials.

Figure B.4: Distribution of PIPs (as percentage of all PIPs) by the number of clinical studies agreed upon



Number of paediatric subjects involved in the clinical trials

The survey collected data on the number of paediatric trial subjects that were involved in phase II and phase III studies, recognising this can be an important cost driver. If a phase had not started, the number of paediatric trial subjects was reported as zero and if the phase was ongoing the number of paediatric trial subjects include the number of patients that had been involved up to that date. The data summary is presented in Table A.18. We also note that in some instances, costs had already been accruing before paediatric trial subjects were enrolled. We understand this to be in relation to preparatory costs of screening as well as difficulties to recruit subjects. For example, the target age of paediatric subjects and the conditions for participation in paediatric trials play a role in recruitment and drive costs.

In our sample, on average, 66 [0-900] paediatric trial subjects participated in phase II clinical trials and, on average, 154 [0-2,000] paediatric trial subjects participated in phase III clinical trials. If the phase was completed, on average, 43 [1-154] paediatric trial subjects participated in phase II clinical trials and, on average, 292 [18-2,000] paediatric trial subjects participated in phase III clinical trials. Note that the median of paediatric trial subjects that participated in completed phases is similar to the median calculated for the overall sample. Moreover, it was found that the majority of paediatric trial subjects are located in the EU.

Table A.18: Number of children involved in Phase II and Phase III clinical trials

	Average	Median	Min	Max	Number of observations
Total number of paediatric trial subjects that participated in the phase II clinical trial(s)	66 (79% EU)	16	0	900	37
Total number of paediatric trial subjects that participated in the phase III clinical trial(s)	154 (57% EU)	54	0	2,000	62
Total number of paediatric trial subjects that participated in the phase II clinical trial(s) - If phase is completed	43 (74% EU)	19	1	154	17
Total number of paediatric trial subjects that participated in the phase III clinical trial(s) - If phase is completed	292 (52% EU)	55	18	2,000	21

Table A.19 presents a breakdown of the average estimated cost per subject. These calculations are based on values of individual PIPs and using data on both completed and incomplete R&D phases. This yields an average cost per subject of €377k and a median cost estimate of €77k for phase II; for phase III, we calculate an average cost of €244k and likewise a median cost estimate of €77k. The median estimates may be considered a more helpful indication of cost per subject.³⁸ We however recognise that the sample dataset underlying our cost estimate per subject for phase II and phase III trials involves large variations and thus significant uncertainties remain in these cost estimates.

Table A.19: estimated cost per paediatric subject recruited in a clinical trial

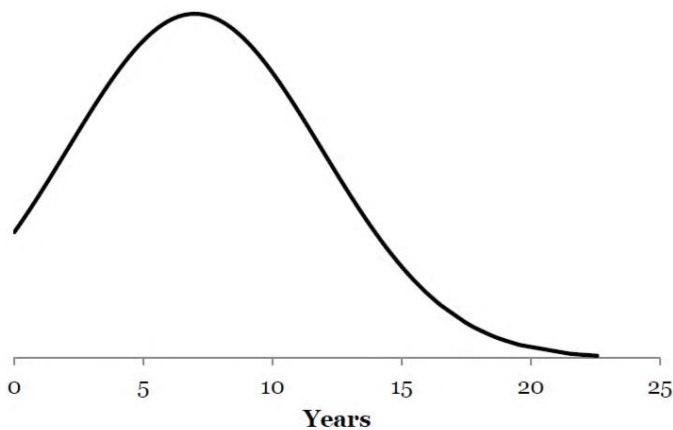
	Average	Median	Minimum	Maximum	Number of observations
Phase II	€377k	€77k	€20k	€3.5m	27
Phase III	€244k	€77k	€1k	€4.0m	44

Duration of a PIP

The average planned duration of a PIP, from the date of initial application to the planned completion date, is 7 years [0-23] (calculation based on EMA data) with a considerable variation between the expected duration of PIPs – as illustrated in Figure B.5. It is also expected that the average duration of PIPs that are discontinued, based on the date of submission up to the point that they are discontinued, will be lower than 7 years.

Figure B.5: Distribution curve of the planned duration of PIPs in years

³⁸ The average cost estimates calculated using data on both completed and incomplete R&D phases are significantly higher than estimates that can be calculated using data on completed phases only: for phase II, the average number of subjects is 43, the average estimated cost of the trial is € 7.3m, and thus the average cost per subject is €170k. For phase III, the average number of subjects is 292, the average estimate cost of the trial is €15.7m and the average cost per subject is only €54k.



Moreover, an analysis of the average duration of PIPs sorted by the initial submission year shows that the PIPs filed in the initial years of the Regulation, especially in 2008, had a lower than average expected duration. It may well be that those PIPs were less burdensome (in cost and time) as many of these products had generated significant clinical data, and probably originate under Article 8. It should be noted that because only a relatively smaller number of PIPs were submitted in the first years following the enactment of the Paediatric Regulation, it is likely that the overall effect on estimated cost to industry is small.

Therapeutic areas

The cost of filing and executing a PIP is also related to the therapeutic area. For example, it will be more challenging to recruit clinical trial subjects for some indications in certain therapeutic areas than others, resulting in a notable difference in the average number of paediatric subjects involved in the trial. Details of the costs per therapeutic areas are given in section 2.2.4.5 of the economic study. However it should be noted that those cost figures are merely indicative as it relies on a small number of observations and cost drivers other than the therapeutic area may be at play.

Collaboration with networks

Based on the survey results, 18% of PIPs involved a collaboration with a research network. This included informal networks and consultations with paediatricians and formal networks such as the European Paediatric Formulation Initiative (EUPFI), the Task-force in Europe for Drug Development for the Young (TEDDY), the Medicines for Children Research Network (MCRN), and the Innovative Therapies for Children with Cancer (ITCC). In some cases, there may have been a monetary benefit from engaging in research collaborations. It is likely

that collaborations with academic partners not only help to drive more effective paediatric research but also test drugs within the paediatric population at a lower cost.

1.3 Comparison of costs under the US legislation

The US has a different approach than that of the European Union to engaging with the pharmaceutical industry. The US recognised the need for a paediatric exclusivity provision in the FDA Modernization Act in 1997. Later, the Pharmaceuticals for Children Act (BCA, 2002) and Pediatric Research Equity Act (PREA, 2003) came to represent a two-tier system and the major cornerstones of the paediatric medicine development in the US. The FDA Safety and Innovation Act (FDASIA) made BCA and PREA permanent in 2012. While PREA authorises the FDA to require paediatric assessments (triggered by a new drug application, or new indication, active ingredient, dosage form, etc and hence mandatory), BCA provides a financial incentive to companies to voluntarily conduct paediatric studies under a paediatric Written Request (WR), often initiated by the sponsor.

The WR considers public health benefits, availability of other medicinal products for the same indication, as well as the actual feasibility of the study design. Note that the initial Pediatric Study Plan (iPSP) is only required in PREA after the completion of adult Phase II trials. In addition, FDASIA also introduced the (transferable) Priority Review Voucher Program for rare paediatric disease indications. The US Government Accountability Office (GAO) published a report in March 2016 and concluded that since innovative medicinal product development typically takes 10 years before regulatory submission can take place, it may be too early to see the results of its effectiveness.³⁹

There are two prominent studies published in the US that calculate the costs of paediatric clinical trials for the pharmaceutical industry (Li et al. 2007⁴⁰; Baker-Smith et al. 2008⁴¹).

Li et al. (2007) selected one drug from each of the following therapeutic areas: cancer, central nervous system, cardiovascular system, psychiatry, endocrinology, gastro-intestinal system, infectious diseases and an 'other' category (based on EMA therapeutic area classifications). The costs for paediatric clinical trials were estimated separately for each drug. This estimation was based on detailed information regarding the clinical trials in the final study

³⁹ GAO-16-319. United States Government Accountability Office: Report to Congressional Committees. RARE DISEASES: Too Early to Gauge Effectiveness of FDA's Pediatric Voucher Program. March 2016.

⁴⁰ Li, J.S. et al., 2007. Economic Return of Clinical Trials Performed Under the Pediatric Exclusivity Program. JAMA, 297(5), pp.480–488. Available at: <http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.297.5.480>.

⁴¹ Baker-Smith, C.M. et al., 2008. The economic returns of paediatric clinical trials of antihypertensive drugs. American Heart Journal, 156(4), pp.682–688.

reports which were submitted to the FDA, and included investigative site costs, contract research organization costs, pharmaceutical company costs, and core laboratory costs in relation to adult/mixed trials. The clinical trials for which costs were assessed included 13 to 1,088 patients, took 6 to 64 months and were conducted on 1 to 118 sites, most of them in the US. Additional details of the trials considered in the estimations included the pre-study preparation and recruitment, data processing, analysis, reporting and drug distribution as well as initiation visits, monitoring, management and close-out of sites. The cost estimation of these factors was based on three separate global cost and procedure benchmarking databases and an internal pricing tool of a laboratory service for those clinical studies that needed core laboratory services. Li et al. provided a 'low' and a 'high' estimate, with the authors stating that, according to their experience, the high estimate is more likely to be accurate in the context of paediatric clinical trials. Note that this approach differs from the approach taken in the current study where product-specific incurred costs were estimated by the sponsors of the trials.

Li et al. concluded that the costs for pharmacokinetic studies range between \$655,139 to \$7.1m (median \$894,941) and between \$655,829 to \$21m (median \$2.3m), respectively, and the costs for an efficacy study range between \$1.8m to \$12.9m (median \$6.5m) – see also Table 8 for adjusted cost estimates. This resulted in a range of costs for a WR between \$5.1m and \$43.8m (median \$12.3m), which included 1 to 8 clinical trials per request. After adjusting for macro-economic changes this amounts to a cost per WR between €5.6m and €47.9m (median €13.5m). Based on the data presented in the study of Li et al., we calculate that the median cost per enrolled subject is €42.7k, which is lower than the median costs presented in this study in relation to phase II and phase III R&D trials, which is € 77k.

Some of the authors of the first study conducted a second analysis, focussing on nine drugs for the same indication, hypertension (cardiovascular diseases), in order to achieve a general estimate of paediatric trial costs for drugs with this clinical indication (Baker-Smith et al. 2008). From 1997 to 2004, the FDA received final study reports for 12 antihypertensive drugs, and the authors included in their sample all of those drugs which had a completed final study report (24 in total) and were comparable in their clinical trial design, being all orally administered. 75% of the studies were conducted in children, the remaining 25%, which are bioequivalence/bioavailability studies, were conducted in adults. The authors estimated the costs and cash-outflows with the same method as in their first study, providing low and high estimates for each clinical trial. As in the previous study, the costs included investigative site costs, contract research organization costs, pharmaceutical company costs, and core laboratory costs. Not included were the costs of formulation changes, marketing costs and distribution costs. The clinical trials for this sample of drugs included 16 to 441 patients over 6 to 50 months and were conducted on 1 to 78 mostly US sites.

Estimated adjusted-costs per WR for these nine range from €4.2m to €15.5m (median €6.6m), which includes the cost of bioequivalence/bioavailability studies. 41% to 73% of costs of clinical trials were related to coordination (linked that the cost incurred by a coordinating centre), including the cost of site management and project management. The adjusted-median cost for efficacy and safety clinical trials, similar to phase II trials, is lower for the study of Bakker-Smith et al (€4.7m) which looks at hypertension than the adjusted-median costs presented in Li et al. (€7.1m), which covers a range of drugs. Both figures are higher than the estimated median costs for phase II R&D trials that is presented in this study (€1.7m). Median costs for efficacy and safety clinical trials and pharmacokinetic studies per subject (see Table 8) are roughly less than half of the median cost estimates presented in this study in relation to phase II and phase III trials (€77k).

The recalculation of the financial cost data per trial from the sample dataset and present the results along with the study of Li et al. The cost elements of phase II, phase III and other R&D costs were then aggregated to reflect the overall R&D cost related to paediatric drug development and adjust this cost estimate for inflation and exchange rates. This average cost estimate was then compared with the average cost estimate of presented earlier in the current study. Figure B.6 presents an overview of the adjusted cost data of Li et al. in various therapeutic areas. Whilst the average costs presented in the current study are intended to reflect average cost to industry, it should be noted that the data from Li et al. is not intended to be representative of the industry. The adjusted average cost estimate based on the data of Li et al. amounts to €21m, higher than our €18m cost estimate for phase II, phase III and 'other' R&D costs. It should be noted the high variation in costs related to paediatric investigation for different drugs: ranging from €6m to €48m. However, when the US and EU cost estimates are compared per study, the variations become less pronounced (Figure B.7). The average cost of a paediatric study according to Li et al is €7m, with individual therapeutic areas ranging from €3m to €11m, while the calculated cost per study is €6m in the current study.

Figure B.6: Estimated costs of paediatric investigations

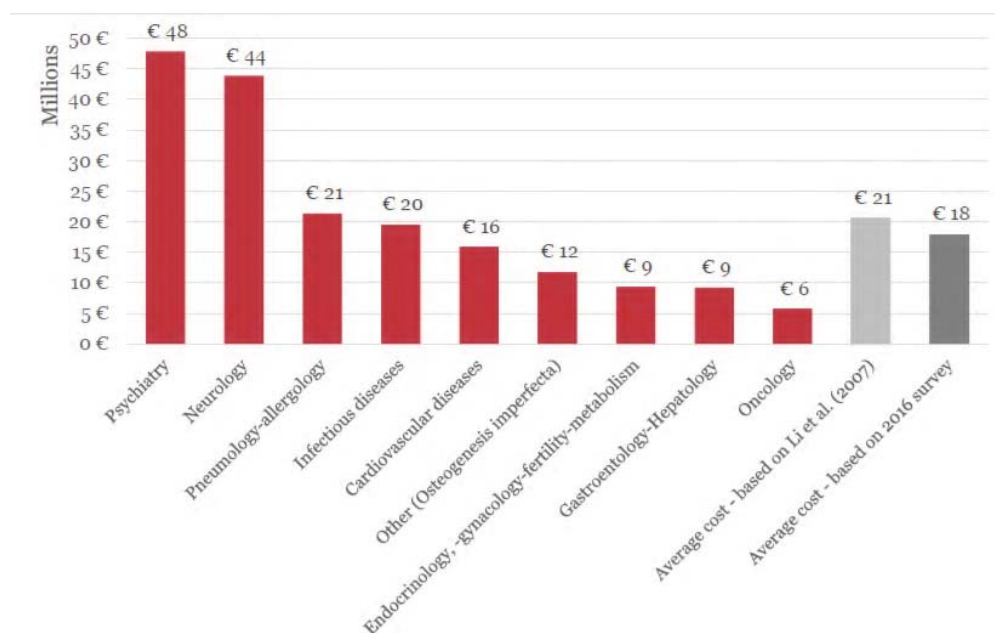
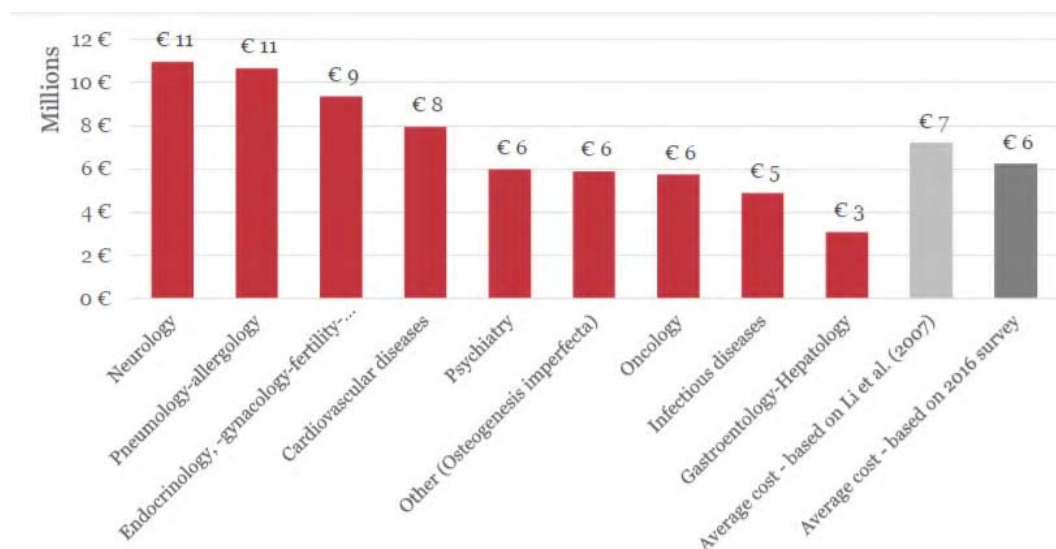


Figure B.7: Estimated costs of a paediatric study



1.4 Comparison of R&D costs of paediatric trials with adult population trials

Two studies specified particularities of paediatric clinical trials, which are likely to lead to higher costs for these trials compared to the ones with adult patients (Mathis & Rodriguez 2009⁴²; Upadhyaya et al. 2009⁴³). These included the limited number of patients available for trials, since the physiological changes in children require conducting separate studies for different age groups and to assess the patients' unique growth and development regularly during clinical trials. One industry survey respondent remarked that “the many scientific, ethical and practical complexities involved have traditionally made paediatric studies more challenging, costly and time-intensive than those conducted in adults”.

This suggests that cost per trial subject is likely to be higher for paediatric studies. In this section we compare the average cost estimates presented in this study with that available in the literature looking at the cost involved in adult/mixed trials.

DiMasi et al. (2016)⁴⁴ provided estimates for industry ‘out-of-pocket’ clinical period costs for investigational compounds. The result shows that the average cost of paediatric phase II and

⁴² Mathis, L. & Rodriguez, W., 2009. Drug therapy in pediatrics: A developing field. *Dermatologic Therapy*, 22(3), pp.257–261.

⁴³ Upadhyaya, H.P., Gault, L. & Allen, A.J., 2009. Challenges and Opportunities in Bringing New Medications to Market for Pediatric Patients. *Journal of the American Academy of Child & Adolescent Psychiatry*, 48(11), pp.1056–1059.

⁴⁴ DiMasi, J., Grabowski, H., and Hansen, R. (2016). Innovation in the pharmaceutical industry: new estimates of R&D costs. *Journal of Health Economics*, 47.

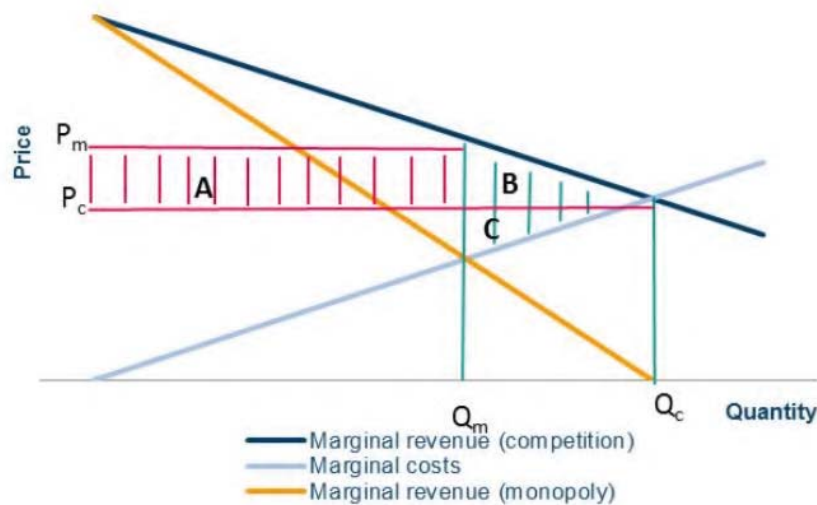
phase III clinical trials are only a small fraction (14% for phase II and 7% for phase III) of the cost estimates published by DiMasi et al. One possible explanation for the cost differential is that adult clinical trials may involve a relatively larger number of trial subjects. Also, clinical trials for adult population is more likely to involve double blind placebo controlled confirmatory studies, which, depending on the therapeutic area, may differ in size and scope. Additional analysis of available evidence is needed to compare the costs per subject of paediatric trials with those of adult population trials. More details can be found in section 2.4 of the economic study.

2. Analysis of the economic value of the rewards/incentives

The assessment of the economic value of the reward is based on the following key assumption. As a result of the market exclusivity extension, there is a delay in the shift from the (higher) monopoly prices to the (lower) competitive market prices. This delay in the change of price is calculated to represent the economic value of the rewards.

The standard economic theory states that in a competitive market situation, the price of a product equals the marginal costs of that product. The main explanation for this equilibrium is that, due to the price pressure from other competitors, it is not possible for a company to charge a relatively higher price without losing market share. In a situation of market exclusivity competitive market pressure is absent (or very small) and the monopolist is able to charge above the marginal cost price. This higher price corresponds, in comparison with the competitive market situation, with a lower quantity of product sales. This model is presented in Table A.20.

Table A.20: Monopoly vs competitive situation



Note in a competitive situation, the price (P_c) equals the marginal costs and results in a certain quantity of sold products (Q_c). In a monopolistic situation, the monopolist can charge a higher price (P_m) which leads to a lower quantity sold (Q_m). The underlying assumption is here that a company, who wants to maximize the profit, should set the output (quantity) on the level that the marginal revenues equal the marginal costs.

A monopolist benefits from a higher price but, because prices are relatively higher, forgoes some opportunity to sell. The ‘surplus’ is represented by rectangle A (profit for the company) and triangle C (loss for the company) in the figure above. As a result of the monopoly price and quantity, consumers lose a ‘surplus’ of rectangle A and triangle B in the figure.

- Rectangle A represents the profit accrued by the monopolist and the loss for the (potential) consumer.
- Triangle B and C represent the deadweight loss from monopoly power and loss to society: even if the monopoly profits are regulated to zero, the surplus for the society as a whole is lower than in a competitive situation.⁴⁵

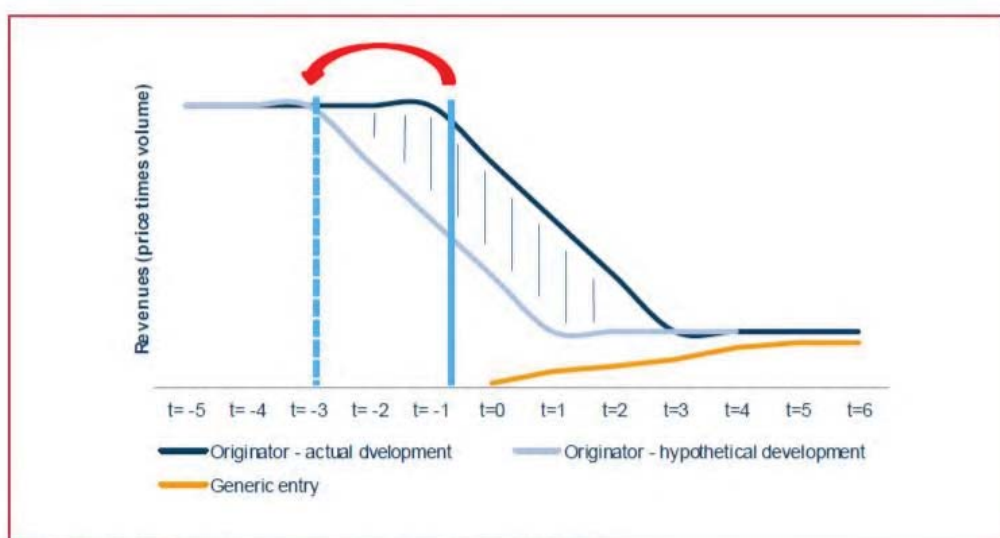
The standard economic theory as described above is used to capture the impact from the Paediatric Regulation on pharmaceutical companies and on the healthcare system. In this case, the market is first represented by a monopolist that has exclusivity rights and then shifts towards a competitive market situation as a result of generic entry. In the situation of the Paediatric Regulation, the granted exclusivity rights prolong the monopolistic market situation.

⁴⁵ Pindyck, R.S. and Rubinfeld, D.L., ‘Microeconomics’, 5th edition, 2001, section 10.4.

In order to assess the ‘economic value’ of the rewards, two dimensions need to be taken into account.

- The rewards compensate the originator companies with a longer period of protection from the introduction of competing generic medicines and policies which favour the prescription of generic medicines.
- Because the introduction of generic medicines is delayed, society does not benefit from increased competition and lower prices for the duration of the exclusivity extension.

Figure B.8: Calculation of the economic value



Note that in this study t represents 1 quarter (3-month period)

Figure B.8 shows the actual revenue development of an originator product with a reward. The revenue starts to drop at the moment the exclusivity right ends (vertical line at $t=0$) and a generic producer enters the market. At a certain moment ($t=5$) the market reaches a new equilibrium. Without the additional reward the generic producer can enter the market earlier and the revenue drop of the originator will start (six month) earlier. In combination with the actual revenue development of the originator company, the shaded area represents the ‘economic value’. This is a temporary ‘benefit’ for the originator company and a temporary ‘loss’ for the society. In line with the approach of DG COMP (2009), we shift the actual curve (“Originator – actual development”) six month to the left (“Originator – hypothetical development”) and estimate the difference between the two curves.

Note that this is a simplified model for illustration purposes. In reality, there are several other factors which influence the economic value of the reward which may affect the revenue/price drop curves across EU Member States.

- When interpreting national sales data from comparative perspective, it is important to account for the proportion of patients on treatment and the manufacturer price. The originator company may follow a different pricing strategy by anticipating the moment the exclusivity right expires and lower the price gradually or keep the price stable for a longer period if there is still no generic product.
- The economic value of the reward can also be influenced by the availability of competing (generic) products which function as an alternative or substitute. If there is no generic medicine available, the revenues of the originator product may remain stable after the expiration of the exclusivity right. This factor also relates to the existence of clinical guidelines and the willingness of patients to switch between different brands of medicines. A recommendation on using a particular drug is very likely to have a positive effect on the sales of the drug. The results from the interviews conducted in this study confirm that in some Member States patients want to continue using the (branded) medicines they are familiar with, despite a substantial price difference. If this is the case, the pressure on the originator company to lower the price is limited.
- Finally, national (reimbursement) policies and regulation are important factors that influence prices. European countries use different approaches regarding the pricing of generics. Some countries (e.g. France) use prescriptive pricing (regulated prices), other countries (e.g. Sweden, Netherlands) apply free pricing³⁶. Different approaches to the pricing of generics among European countries can lead to substantial variation between originator and generic prices³⁷. Also, countries may emphasise the prescription of generic products through national policies (e.g. Sweden³⁸). Beside that there exist incentives to keep the originator price high in certain countries, due to the fact that other countries use those prices as a reference price in determining the reimbursement price they pay.

Details of the calculations are provided in Annex 3.

2.1 The six months SPC extension

The analysis is based on IMS Health data provided by the European Commission for period between 2008-2014 (the last available data point is the 3rd quarter of 2014). The scope and limitations of the dataset are described in Appendix C of the economic study. The analysis in this report covers products which (i) received a SPC extension in the period between 2007-

2012 and (ii) lost their exclusivity before the third quarter of 2014. This choice for this period is related to the need to have enough observations in the data after the loss of the exclusivity. The data available for the study covered 14 products which received the SPC extension in this period. However, five products received the reward but were still under protection in the third quarter of 2014. For one product, available data did not allow to make a distinction between protected and non-protected products with an SPC extension. See section 3.2 and Appendix C of the economic study for a detailed description. The remaining eight products are used in the analysis. The analysis also builds on interviews with pharmaceutical industry.

Over the period 2007-2015 the SCP reward was granted to 32 different medicinal products. In total there were 311 extensions, as not all medicinal products received the six-month extension in each Member State. The data available for the study included 14 products but for the analysis only used eight products were included. Products are excluded from the data analysis due to patent expiry after 2015 and in one case a product was excluded from the data analysis due to differentiation issues; the SPC product could not be isolated from the non-SPC products.

In terms of the geographical spread of the SPC extensions, there is a clear distinction between the Member States who joined the EU after 2003 (EU-13) and the other Member States (EU-15). The countries with the highest number of SPCs are located in West and North Europe (EU-15). According to interviewees, this relates to original design of the patents in the EU-15 Member States: SPC extensions fit better with the patents granted in these Member States. See Figure B.9.

Figure B.9: Geographical spread of the SPC in the EU (2007-2015)



2.1.1 Generic entry

Details of the analysis are provided in section 3.2.2 of the economic study.

Generic entry - the analysis conducted shows that for all eight products there exists generic entry. The number of entrants varies between products and countries. The largest numbers of entrants can be found in countries such as France, Germany, and Italy. However, other countries, like The Netherlands, Ireland, and especially Sweden, also show a substantial number of generic entrants, although their number varies across the different drugs.

Time to enter –the data shows that the average time it takes a generic producer to enter the market with a generic product (after the loss of exclusivity) is relatively short. Again, there exist substantial differences between countries and products. For all products there is generic entry in the first quarter in at least five countries. In Germany, Italy, Ireland, the Netherlands, Sweden and the UK market entry is visible for nearly all products (with a very few exceptions) in the first quarter after the loss of exclusivity.

2.1.2 The envisaged price change

In a competitive market, the pressure of generic entry is expected to lower the prices of branded products after the loss of exclusivity. The change in price level prior and after the loss of exclusivity was assessed⁴⁵ (if possible: 1-4 years after the loss of exclusivity). Please note that again there exist significant differences between countries and products.

The data analysis shows that the price drop of branded products often starts in the first quarter after the loss of exclusivity. However, this price drop is often relatively limited (up to 10-20%). During the first and second year (after the loss of exclusivity) the branded prices decrease further, but with larger differences between products and countries. For example, in the Netherlands the price drop after two years varies from 42-60%, while in Germany this varies between 4 and 24%. When the branded prices are weighted for the sold volumes, the price drops in the end are often substantial (in some cases up to > 95%). The underlying data shows that branded products often keep a higher price than the generic competitor but that the sold volumes of branded products are very low.

For most of the selected products, the starting price of the generic entrant after the loss of exclusivity is significantly lower than the price of the branded products. Italy is an example of a rather aggressive generic pricing strategy: in the first quarter after the loss of exclusivity the generic prices are 30-40% of the original branded price (relative price reduction of 60-70%). At the end of the data period (Q3/2014), a lot of generic prices are 10-30% of the original branded price.

2.1.3 The level of generic penetration

The loss of the exclusivity results in the entry of relatively cheap generic products and (often) in a substantial drop in the prices of branded products. As can be expected, the generic entry will also have an influence on the market share of the originator product. In the data analysis, we assessed the level of generic penetration: the relative share of generic products in the total volume (branded and generic products) in the period after the loss of exclusivity.

The findings show that the level of market penetration of generic products differs per country and per product. In some cases, the share of generic products in the total volume is above 70-90% (e.g. Sweden and the Netherlands), while in other cases the level of generic penetration is much lower (e.g. Belgium and Italy). There seem to be two main explanations for these differences. First, the national policies in relation to the prescription and reimbursement of generic products differ. In the interviews conducted it was confirmed that, especially in

Sweden and the Netherlands, the use of generic products is lobbied for after the loss of exclusivity. For Italy, several interviewees indicated that the ‘push’ towards generic drugs is much softer and that patients often have a preference for the branded product they are familiar with. Second, the generic penetration seems to be related to the price strategy of both the generic and the originator product. Details on the substitution effect due to generic entry can be found in section 3.2.5 of the economic study.

2.1.4 Economic value of the SPC extension

Details of the calculations and of the limitations are provided in sections 3.2.6-3.2.8 and in Annex 3 of the economic study; Figure B.10 shows the economic value per product.

Figure B.10: Economic value per product

INN (# of included countries)	6-month revenue	Revenue with SPC ext.	Revenue without SPC	Economic value	Economic value as % of 6-month revenue
Drug A (8)	██████	€ 270,309	€ 212,187	€ 58,122	50.7%
Drug B (8)	██████	€ 65,646	€ 51,541	€ 14,105	43.4%
Drug C (7)	██████	€ 26,271	€ 16,916	€ 9,355	49.5%
Drug E (11)	██████	€ 540,988	€ 394,491	€ 146,497	67.8%
Drug F (10)	██████	€ 458,454	€ 353,237	€ 105,217	61.7%
Drug G (9)	██████	€ 451,678	€ 338,457	€ 113,221	58.1%
Drug H (9)	██████	€ 208,701	€ 177,518	€ 31,183	39.0%
Drug I (4)	██████	€ 189,866	€ 150,317	€ 39,548	46.0%
Total	€ 913,432	€ 2,211,913	€ 1,694,664	€ 517,249	56.6%

Based on IMS Health data. Notes: (i) between brackets is the number of countries covered in the analysis; (ii) revenues include both adult and paediatric usage; (iii) Drug D was eliminated from the analysis.

However, due to limitations in the availability of data and in the data itself, it was not possible to calculate for all countries and products the ‘full’ economic value of the reward.

The available data were used to make an extrapolation in order to assess the (magnitude of the) ‘full’ economic value of the reward. This extrapolation is based on assumptions and that the actual economic value may differ from our estimations. The extrapolation is done in two steps.

- The first step is to estimate the economic value of the reward for the countries that are missing in the current set of eight products. Although in these countries an SPC-extension was granted, the dataset available for the study did not include data on these

countries. Based on the 'revenue and economic value per capita'⁴⁶, the 6-month revenue and the economic value for the missing countries was estimated⁴⁷. The new estimated economic value, €628m, increased with 22% compared to the original estimated economic value of €517m.

- The second step in the extrapolation is to include the (four) products for which the period of exclusive rights, including the SPC-extension period, ended within the research period taken into account (December 2015), which is after the date of the dataset available for the study (third quarter 2014). Drug D, for which the data did not allow to make a distinction between protected and non-protected products with an SPC extension, was also included. Based on the total population in the specific countries associated with the specific year in which the patent expires and 'revenue and economic value per capita' of the eight products in our dataset, we made an estimation of the 6-month revenue and the economic value of the SPC reward for the products. Based on this second step in the extrapolation, the adjusted economic value, €926m, increased with 79% in comparison to the original estimated economic value of €517m. Please note that the therapeutic areas of autoimmune diseases, diabetes mellitus and antipsychotics are not covered in the original set of eight products, which increases the uncertainty of the extrapolation.

With regard to estimating the economic value, a number of specific considerations need to be made:

- It is important to emphasise that the analysis is to some extent determined (and limited to) by the type and quality of the data that is available. As the steps for the extrapolation of the data show, the dataset available for the study is not including data on all products and /or countries which - in an ideal situation - would have been part of our dataset. The need to use assumptions results in uncertainty about the estimations. This margin of error in (especially) the extrapolation is strengthened by the fact that individual medicines often differ significantly in terms of strategic (pricing) behaviour of the originator and generic company and underlying market dynamics.
- Further, it is uncertain to what extent the available data is reflecting a fully realistic situation. The list prices for example (as used in the IMS Health database), are hardly

⁴⁶ The economic value per capita is based on the calculated economic value per product and country, divided by the total population in the specific countries associated with the specific year in which the patent expires. The population is based on Eurostat-data.

⁴⁷ For the missing countries, the economic value is calculated by multiplying the average 'economic value per capita' with the population size.

used in practice. In some countries additional margins are added on top of the list prices for service providers, such as for example pharmacists. At the same time, pharmaceutical companies may negotiate reimbursement prices with national health authorities and health insurances, which may result in a discount on the prices of the medicines. Despite these opposite price dynamics, we expect that the list price as presented in the IMS Health database is an underestimation of the ‘real’ price which at the end is paid by the health care payer. This would imply that also the calculated economic value of the SPC reward is an underestimation of the actual economic value. Uncertainty also exists in relation to the reported volumes in the IMS Health dataset. For some products and/or countries the dataset (only) contained hospital or retail data. This implies that in reality the volumes (and also the revenues) are higher than the reported values in the dataset and that the calculated economic value of the SPC-reward is an underestimation of the actual economic value. Within the scope of this study (and the available dataset), it was not possible to assess the magnitude of these (presumed) underestimations.

- A third consideration is that a substantial share of the economic value of the SPC-reward lies in the future. The research shows that a lot of SPC-extensions are granted in the last couple of years, but (due to the fact that the product is still under protection) not ‘effectuated’ yet. Especially in 2015 a lot of decisions on SPC-extensions are taken, which will materialize in the upcoming years.
- A final consideration is that the estimated size of the SPC-reward (i.e. the estimated economic value) does not always have a direct link to the ‘efforts’ (investments, R&D, etc.) the pharmaceutical companies made during the 2008-2014 period. The SPC-reward is linked to a specific product, while efforts and investments of pharmaceutical companies are often spread over a broad portfolio of products, activities and investments.

2.2 *The Orphan reward*

Until mid-2016, four orphan-designated products have successfully fulfilled the requirements of article 37 of the Regulation, thereby becoming eligible for the orphan reward.

The data available for these four products is limited in scope and ‘quality’. This is mainly due to the fact that all four products are still under protection (no generic entry).

Due to the fact that the four products are still under protection, it is not possible to estimate the economic value of the orphan reward. At the same time, a projection of the current data towards the moment of loss of exclusivity in the future is unreliable. This is mainly related to

the data availability and the uncertainty about the effects of generic entry (ie, will there be generic entry? what will be the effect on the prices?).

2.3 The PUMA reward

Until mid-2016 only 2 PUMAs received a positive opinion from the EMA's Committee for Medicinal Products for Human use (CHMP).

While it is not possible to have a meaningful calculation of the value of the PUMA reward, the economic study develops in section 3.4.1 a methodology which could be used when more products will be authorised and information will become available.

3 Direct and indirect benefits

In addition to data collected via the survey to industry, the analysis builds on a two-stage survey (Delphi) to expert stakeholders. The survey questionnaire was sent to experts from across the EU, with 116 people ultimately completing the survey (Phase I Delphi), although some respondents did not answer every question. The background and paediatric speciality of Phase I and Phase II participants are presented in Appendix D. The survey to expert stakeholders was developed based on an exploratory telephone consultations and pilots to uncover issues linked to social and broader economic impacts in the paediatric drug development value chain. The survey collected qualitative and quantitative estimates for the various dimensions of the impact as well as provided a set of open questions to identify further benefits of the Regulation and their impact channels.

The design of the survey questions builds on the evidence gathered via the systematic literature review and the secondary data analysis. This provided an outline of potential benefits/impact drivers of the Paediatric Regulation. The focus of the social impact analysis is to estimate to what extent better treatment (due to more effective medicinal products) reduces the costs of paediatric healthcare treatment due to shorter periods of hospitalisation or fewer adverse drug reactions (ADRs). This may lead to significant reductions in paediatric healthcare expenditure and increased overall savings from reduced child morbidity and mortality. We consider possible monetary and non-monetary impacts. We focus on the following dimensions:

- Availability of and access to medicines result in better treatments and better QoL for children
- Reduction of child-health expenditure, savings from reduced morbidity/ mortality, increased school attendance, and decreased time taken off by parents for caring for their children and adverse drug events

To estimate the monetary value of social savings from improved medical treatment of children as a result of the Paediatric Regulation is very difficult. Vernon et al⁴⁸ use US data on discounted life-years, then authors calculate value-added life-years. It is assumed that if off-labelling would have been on-labelling, this would have resulted in a 1% reduction of mortality. The authors then calculate the value of this reduction in mortality using discounted life year valuations. Therefore, using data on hospitalisation and mortality rates in the EU one could refine the model. It should be noted that life year calculations differ across countries. The [EuroVaQ project](#) looking at the European Value of a Quality Adjusted Life Year provides a starting point on computing life year valuations across the EU.

An economic assessment of the second-degree effects of the Regulation, notably, on the research framework created, activities of specialised research centres and CROs, public-private funding created for paediatric medicine, new research knowledge established, and networks formed. A good example is the European Network of Paediatric Research that aims at fostering high-quality paediatric research; helping with the recruitment of patients for paediatric clinical trials; and enabling collaboration between stakeholders.

3.1 literature review

One of the chief aims of the 2007 EU Paediatric Regulation is protecting the health of children by improving the availability of medicines and dosage information for children. The regulation also intends to stimulate research into paediatric medicines. Thus, the regulation is directly linked to societal impacts such as improved health of children, decreased disease burden and costs to national health systems. Greater availability of published data on the efficacy and safety of medicines will potentially lead to better use of medicines in children.⁴⁹ For instance, benefits are expected from new paediatric indications, inclusion of special (class) warnings, specification of dose regimens, timely development of paediatric friendly formulations, and better quality of the clinical evidence.⁵⁰

One of the direct consequences of the new regulatory requirements such as PIPs, even for authorised medicinal products that are currently protected by patents, is the development of

⁴⁸ Vernon, J.A. et al., 2012. Measuring the patient health, societal and economic benefits of US paediatric therapeutics legislation - Technical Appendix. *Pediatric Drugs*, 14(5), pp.283–294.

⁴⁹ Hoppu, K. et al., 2012. The status of paediatric medicines initiatives around the world-what has happened and what has not? *European Journal of Clinical Pharmacology*, 68(1), pp.1–10.

⁵⁰ Stoyanova-Beninska, V. V. et al., 2011. The EU paediatric regulation: Effects on paediatric psychopharmacology in Europe. *European Neuropsychopharmacology*, 21(8), pp.565–570.

formulations and dosages more appropriate for paediatric age groups.⁵¹ However, of all the approved PIPs, only 26% and 35% of medicines included trials in young infants and neonates, respectively (Hoppu et al. 2012). Moreover, some authors also argue⁵² that PIP decisions can lead to the recruitment of vulnerable children to questionable studies. A similar observation has been made with regard to the PREA in the US. For instance, the necessity of 4 proton pump inhibitor trials for gastrointestinal reflux disease in children has been questioned as there are differences of opinion among clinicians regarding the condition and its diagnosis.⁵³

Between 2007 to 2011, the PDCO made decisions about 682 PIPs; 29 PIPs were completed. Of these, 24 led to new paediatric indications and 77 new formulations. 5 PIPs were completed but did not support the drug's use in children.⁵⁴ Similarly, in the US, the BPCA led to 200 labelling changes and 48 instances of new/enhanced paediatric safety information following paediatric clinical trials.⁵⁵

In terms of drugs for rare diseases i.e. orphan drugs, the Regulation did not result in significantly more market authorisations for orphan drugs with a paediatric indication (58% before and 64% after 2007), but did increase the time required to achieve market authorisation.⁵⁶

Another explicit goal of Paediatric Regulation is the reduction in off-label use of drugs. A study from Denmark by Haslund-Krog et al showed that PIPs covered only a small proportion of the drugs that were being used off-label.⁵⁷ In Finland, the new legislation has a

⁵¹ Challis, J., 2011. The impact of the Paediatric Regulation on existing medicinal products. *Regulatory Rapporteur*, 8(10), pp.4–7 and Olski, T.M. et al., 2011. Three years of paediatric regulation in the European Union. *European Journal of Clinical Pharmacology*, 67(3), pp.245–252.

⁵² Rose, K., 2014. European union pediatric legislation jeopardizes worldwide, timely future advances in the care of children with cancer. *Clinical Therapeutics*, 36(2), pp.163–177. Available at: <http://dx.doi.org/10.1016/j.clinthera.2014.01.009>; Rose, K. & Kopp, M.V., 2015. Paediatric investigation plans for specific immunotherapy: Questionable contributions to childhood health. *Paediatric Allergy and Immunology*, 26(8), pp.695–701. Available at: <http://doi.wiley.com/10.1111/pai.12500>; Rose, K. & Walson, P.D., 2015. The contributions of the European Medicines Agency and its paediatric committee to the fight against childhood leukaemia. *Risk Management and Healthcare Policy*, 8, pp.185–205.

⁵³ Kuehn, B.M., 2012. Laws Boost Paediatric Clinical Trials, But Report Finds Room for Improvement. *Jama*, 307(16), p.1681.

⁵⁴ Turner, M.A. et al., 2014. Paediatric drug development: The impact of evolving regulations. *Advanced Drug Delivery Reviews*, 73, pp.2–13

⁵⁵ Mathis, L. & Rodriguez, W., 2009. Drug therapy in paediatrics: A developing field. *Dermatologic Therapy*, 22(3), pp.257–261.

⁵⁶ Kreeftmeijer-Vegter, A.R. et al., 2014. The influence of the European paediatric regulation on marketing authorisation of orphan drugs for children. *Orphanet journal of rare diseases*, 9(1), p.120.

⁵⁷ Haslund-Krog, S. et al., 2014. The impact of legislation on drug substances used off-label in paediatric wards—a nationwide study. *European journal of clinical pharmacology*, 70(4), pp.445–52.

minor or no impact on off-label use in paediatric inpatients in specialised care: 51% of off-label prescriptions in 2011 vs. 22% in 2001, for new-borns; 21% vs. 5%, for less than two-year-old children; and 24% vs. 3%, for children.⁵⁸ These results show that the needs of neonates and children are not yet being fully met by the Regulation. In fact, out of 682 PIPs at the end of 2011, only 110 involved neonates (Turner et al. 2014).

In Europe, the Paediatric Regulation has also led to the creation of a European network of Paediatric Research at the European Medicines Agency (Enpr-EMA). This consists of national and European networks and centres for paediatric research. However, once the initial support for these networks decreased, most networks have not been able to secure sustainable income because enough trials have not been forthcoming or planned trials have been deferred (Hoppu et al. 2012).

A study of the Utah Medicaid Program in the US estimated that a 6-month extension of patent exclusivity cost \$2.2m over 18 months following the original expiry date and if extrapolated to the entire US population, the cost was estimated at \$430.2m.⁵⁹ Moreover, only a minority of these drugs were prescribed to paediatric patients. Furthermore, the BPCA's contribution was estimated to be 3.6m life years gained over the 1997-2009 period; using \$100,000 per life-year, this yields \$360 billion gross economic benefits according to Vernon et al. 2012 (for more discussion, see Appendix E.1.1).

While there have been more paediatric clinical trials (about 4 times more) over the last decade,⁶⁰ which have greatly contributed to knowledge regarding paediatric medicinal products, certain areas of paediatric pharmacology are still under-explored, such as rare conditions and neonates (see: Turner et al. 2014).

⁵⁸ Lindell-Osuagwu, L. et al., 2014. Prescribing for off-label use and unauthorized medicines in three paediatric wards in Finland, the status before and after the European Union Paediatric Regulation. *Journal of Clinical Pharmacy and Therapeutics*, 39(2), pp.144–153.

⁵⁹ Nelson, R.E. et al., 2011. Patent extension policy for paediatric indications: An evaluation of the impact within three drug classes in a state medicaid programme. *Applied Health Economics and Health Policy*, 9(3), pp.171–181.

⁶⁰ Pansieri, C. et al., 2014. Neonatal drug trials: impact of EU and US paediatric regulations. *Archives of Disease in Childhood - Fetal and Neonatal Edition*, 99(5), p.F438.