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PART 5/6

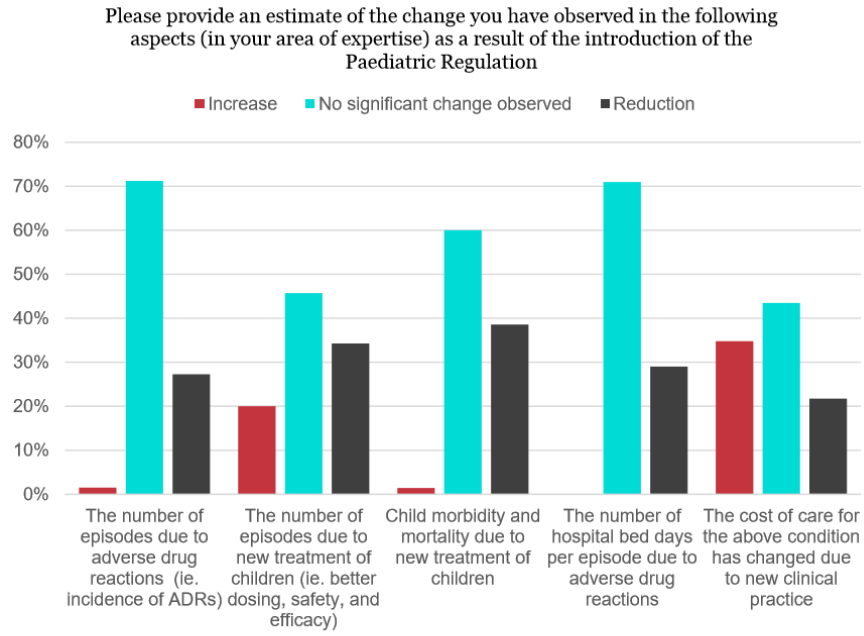
COMMISSION STAFF WORKING DOCUMENT

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}

Table A.28: Health and wellbeing of children and cost of care



Source: Technopolis survey. The number of respondents for each sub-question are: 66, 70, 70, 62, and 69.

This question invited respondents to judge the effect of the regulation on several wider issues, from child morbidity to the costs of care. These wider effects are difficult to identify and measure in any definitive sense, and so we invited people simply to provide an indication of the direction of any changes they had observed in their own area of expertise and which they would feel confident in attributing to the introduction of the regulation. Survey respondents were asked to indicate any observed change (as a result of the Paediatric Regulation) on: adverse drug reactions (ADRs), the number of episodes, child morbidity, the number of hospital bed days due to ADRs, and on the cost of care.

As expected, people found the five questions difficult to answer, however, around 60% of all respondents did provide answers. For each impact type, 40-70% of respondents indicated that they had observed no significant change. While most people had not yet observed any meaningful changes, there was a significant minority of respondents that judged the regulation to have had a positive impact on these different dimensions (i.e. reduction in the value of these indicators). Almost 40% of respondents indicated they had seen improvements in child morbidity in their field, which they would attribute to the regulation.

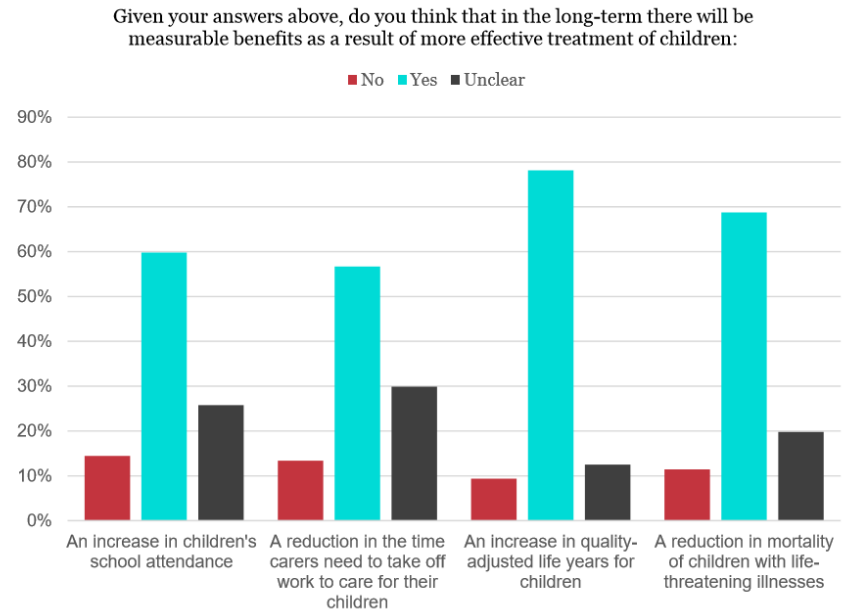
Around 30% of respondents had observed improvements in other impact types, from the incidence of ADRs to the number of related hospital bed days. 20% of the survey respondents find that the number of episodes due to new treatment of children has increased[1] and 35% of

[1] To note that the authors of this paper have no clear understanding why this should be the case and whether respondents may have misunderstood the question: The chart suggests that around 33% of respondents have seen a reduction in the number of episodes as a result of the use of more efficacious paediatric drugs or

the survey respondents indicated that the cost of care had increased due to new clinical practices / prescriptions. New products developed for paediatric use can be relatively more expensive, e.g. there can be cost increases related to the licencing of new medicines. In addition to inviting respondents to indicate the broad direction of travel, the survey asked people to estimate the degree of change they had observed, see Table 24. On child morbidity, 29% of the respondents judged morbidity had improved by 5-10%, 4% argued that it had improved by 10-20% and 6% argued it had decreased by 20% or more. The cost of care was the one dimension where a large minority (35%) indicated there had been a negative impact, with the new treatments and treatment regimens leading to an increase in costs, possibly leading to issues of accessibility.

more appropriate dosing regimens. The chart also suggests that 20% of respondents have seen an increase in the numbers of episodes, as a result of better drugs / dosing. This last point seems counter-intuitive.

Table A.29: Long-term benefits



Source: Technopolis survey. The number of respondents for each sub-question are: 97, 97, 96 and 96.

This question invited respondents to go one step further in considering wider socio-economic impacts. In addition to estimating the impact of the Paediatric Regulation on Health and wellbeing of children and the cost of care, respondents were asked to indicate if, in the longterm, the regulation would have a measurable benefit on:

- Children's school attendance
- Time cares need to take off work to care for children
- Quality-adjusted life years for children
- Mortality rates of children with life-threatening illnesses

The majority of respondents, i.e. 60%, 57%, 78%, and 69% respectively, expect there will be measureable benefits. The remainder of respondents are either unclear about the impact or judge there will be no measurable benefits (9%-14%). Some of the respondents that answered negatively are of the opinion that there are no better treatments on the market at this point in time, and for this reason there can be no measurable improvements in these wider areas.

Another respondent questioned the degree to which long-term benefits attributable to the Regulation will be measurable, while arguing that there will be desirable benefits of many kinds, in terms of more age-appropriate formulations, the facilitation of easier, more precise

dosing, and the availability of paediatric dosing information. Amongst those that were positive with regards to measuring longer-term benefits, several noted that there have been benefits already in disease areas that will eventually have a positive impact e.g. mortality. It was also noted that developments in the treatment of neonates will take another 10-20 years to flow through to measurable impacts, and that such developments are dependent on, amongst other, continued funding.

Various other benefits were mentioned, and these are listed below:

- Benefits to patients and consumer groups
    - Greater awareness on paediatric needs and the importance of testing drugs in the paediatric population
    - Greater awareness in the level of health literacy of the general population - Involvement of the paediatric population in early discussions on drug development –
    - Increase in evidence based prescriptions / dosing information –
    - Availability of more age-appropriate formulations
    - Social benefit in pursuing better medicine for children and access to licensed medication
    - Opportunity for greater awareness about the costs of medical care
    - Early access to new treatments and medications via clinical trials which may also e.g. lead to shortened disease profiles, shorter hospital / treatment periods, better health, and a decrease of health care costs
- Benefits to industry
    - Change of culture, more inclusive focus on developing new and improved medicine for the paediatric population
    - Increase in competiveness within the European market producing benefits to taxpayers and patients, e.g. the EU market is becoming more attractive for FDI because the Paediatric Regulation offers a stable regulatory framework; opportunities for commercial clinical trial investment and attracts research from outside the EU
- Increase in jobs and growth as a result of the increased investment in R&D

3.1 Results from the industry survey

The survey to industry asked to indicate the wider benefits of the Paediatric Regulation. In response, one survey participants noted that, “despite modest achievements so far in terms of rewards, the societal benefits from the Paediatric Regulation cannot be underestimated”.

- Several survey respondents remarked that the regulation has provided access to new and improved medicine. Some respondents referred to an improvement of the quality of care provided to the patients and others referred to better health in children. Moreover, respondents referred to the development of more age appropriate formulation as well as a reduction in off-label use.
- Several survey respondents find that the regulation generated new training, research capacities and knowledge to industry, eg about PK/correct dosing, safety and efficacy of medicines in children.
- Several survey respondents find that the regulation generated new knowledge for prescribers, and has led eg to basing paediatric dosing more on scientific studies, better information on the importance of well tested / approved medications for children and the importance of correct dosing. Other comments included the increase in documentation of error rates in diluting for off-label use and the increase in more updated product information. One respondent finds that the regulation led to the development of dissemination/communication strategies that have addressed laymen and the healthcare professionals' community as well.

- Several respondents commented in the fact that the regulation has improved networks:
    - Increase in the involvement of researchers from academia or public research institutions in paediatric drug development programmes
    - Integration of patients and families into the design and conduct of research and trials increasing their awareness and competence
    - Setup of public-private collaborations sharing of ideas, business, opportunities and innovation
    - Development of collaborations with clinicians enquiring other pharmaceutical and clinical developments
    - Creation of new research networks
    - Some survey respondents remarked that the Paediatric Regulation evoked a change in culture. One respondent reported a significant shift in mind-set within pharmaceutical companies and noted that the regulation helped encourage paediatric development become a more integral part of the overall development of medicines in Europe. Another respondent remarked that the regulation put the paediatric issues at the core of the European agenda and another remarked that it has become an integral part of the overall development of medicines in Europe.

4 Cost benefit model

A generic socio-economic cost benefit analysis (CBA) is a systematic overview, analysis and summary of all impacts (both financial and non-financial) of a (policy) measure, which are deemed relevant for decision making. The aim of a CBA is to determine whether a measure is desirable, i.e. whether from the point of view of the respective decision making person or body the expected benefits exceed those of the expected costs involved – be it at the level of a private organisation, a public body, or society. In cases where alternative paths of action are available, it will also help to identify the most advantageous alternative In the healthcare system, this can be done from different perspectives, taking into account those costs and benefits that impact on a particular entity: the private perspective of a given stakeholder, the patient's perspective, the healthcare system perspective or the social welfare perspective, in which also external costs and benefits are taken into account and transfers (e.g. taxes) are left out. In all perspectives the CBA method calculates the net present value (NPV) of current and future socio-economic cost and benefits of a specific intervention, a project, or a policy and its implementation strategy and measures.

The CBA can be applied - in principle - to any context and policy decision situation, be it in the public arena or a commercial context. It will depend on the decision-maker's perspective which benefits and costs, measured in which fashion, and based on which assumptions, expectations, extrapolations should enter into the overall "equation". It is this feature which allows to test assumptions or expectations and their likely impact, and to choose from alternative application scenarios and options which have the highest likelihood to achieve a particular policy objective.

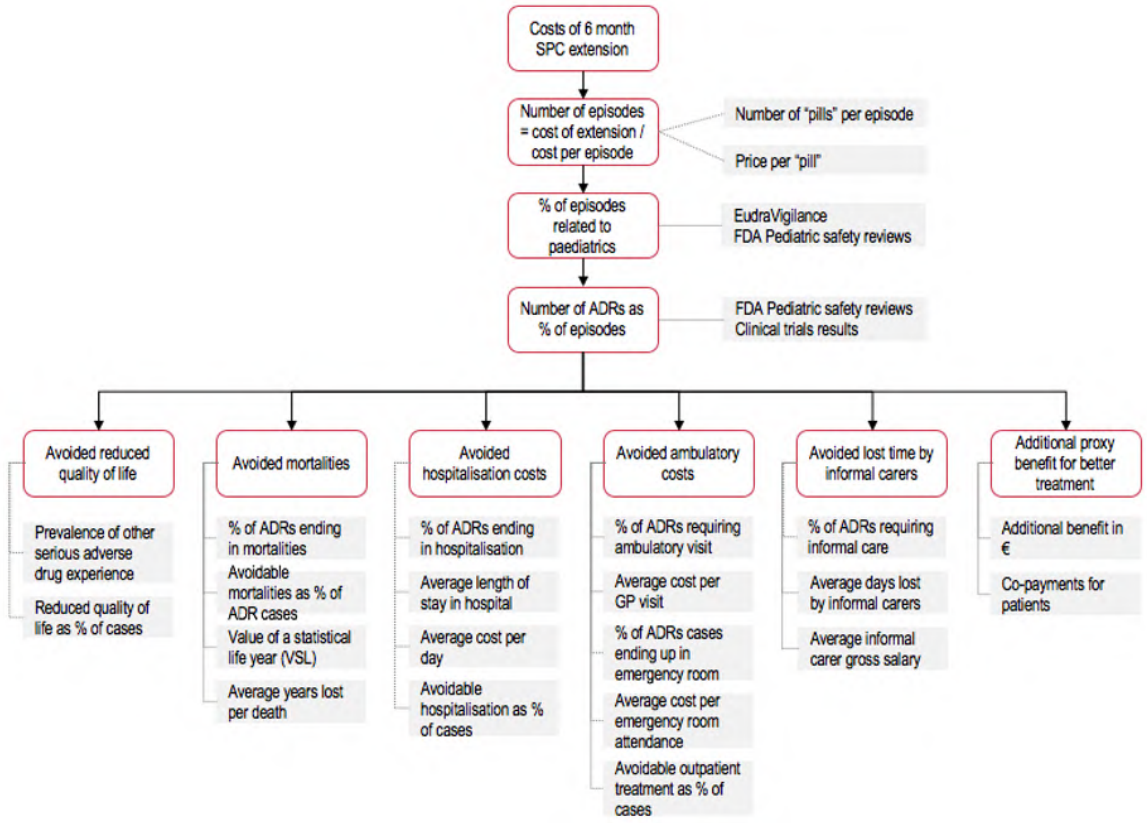
There are very little literature or grey reports available discussing the issue of the potential socio-economic return on the extra monopoly rent reaped by pharmaceutical companies holding a market authorisation for a medicine which was awarded an extra 6-month SPC after successful execution of a PIP. These extra costs accrue to the healthcare system and to each individual patient concerned – either directly or via contribution to healthcare related taxes and health insurance payments. It is assumed that children which take the medicine in question, and indirectly others, will considerably benefit from better treatment outcomes. These benefits may relate to:

- Improved paediatric care through added precision in the use of pharmacotherapy in paediatric populations
- Reduced ADRs and burden of paediatric diseases
- Shorter periods of hospitalisation.

In return, these benefits may contribute to lower consumption of medicinal products through better targeting of treatment. However, it is also possible that these benefits will lead to an increase in the consumption of medicinal products as a result of the potential improved access to medicines.

This means that more children could be treated with the right medicine. Improved access to medicines may also imply marginally lower liability cost for health service providers (resulting in lower insurance premiums). The following graph (Figure B.11) summarises the main elements of the cost-benefit model:

Figure B.11: main elements cost-benefit



Details of the model are provided in Appendix E.3 of the economic study.

4.1 Cost-benefit assessment of selected medicinal products

This analysis represents a bottom-up approach, based on a detailed benefit model and cost data ('economic value'), and covers eight medicinal products for which sufficient data were available. Seven are for treating a chronic disease and one for an acute disease. They cover a diverse spectrum of seven different diseases. Five of these are used on-label for certain age groups of children, while for three drugs, although PIP studies were negative, data indicate their continued use in children.

Of these eight products, five show low to marginal percentages of all episodes related to paediatrics (0.09%; 0.21%; 0.33%; 0.83%; 1.48% - in absolute numbers: 323; 770; 1,017; 3,209; 4,351). Three have with 7.4%, 9.5% and 37.6% significant shares (absolute: 12,644; 206,986; 405,096). Making use of FDA and EMA statistics and paediatric safety review reports for the products included, the absolute numbers of ADEs (note: not ADRs, the numbers of which are lower) for the eight drugs were estimated at 0.17, 0.25, 0.87, 1.27, 1.47, 2.00, 4.22, 34.30.

The values of serious paediatric ADE reports as percentage of all paediatric episodes, ranging from 0.0002% to 0.41%. Only for a single drug deaths of children were reported as ADEs. Relating those data to a six-month period, an absolute number of 0.25 deaths due to an ADE was estimated. Note that these figures are derived from mathematical computations and therefore are not reported in integers. In the literature, there is quite some discussion around sometimes significant underreporting of ADRs, ADEs and medication errors. On the other hand, using ADE data leads to overestimation of ADRs. Also, FDA safety reports use prescriptions per patient (sometimes over 10 and more years) as a reference base, which also leads to overestimation of ADEs on a treatment episode base in case the patient obtains more than one prescription during this period.

Furthermore, both EMA and FDA note some overreporting (double reports on the same ADE), particularly on deaths, and some error in reporting. For the benefit calculations, the ADE data is adjusted upwards by 100% (doubling) data for deaths, and 200% to 400% (3 to 5 times) for less serious events to account for likely underreporting.

4.2 Estimating monopoly rents

To estimate the true costs to national/regional (government) payers and statutory health insurances, monopoly rents for the pharmaceutical industry need to be increased by the extra revenue accruing to other beneficiaries like wholesalers, pharmacies as well governments (wherever VAT or sales tax is levied on medicinal products). In Germany, e.g., this additional monopoly rent amounts to 32% of industry monopoly rent. Because in some countries no wholesalers may be involved or no sales tax is levied on prescription medicinal products, it is assumed that, on average across the EU, the monopoly rent to industry

accounts for 87.5% of overall rent, and only 12.5% accrue to other beneficiaries. This renders an extra cost to society estimate of €590m. In order to arrive at the cost to health system payers (national or regional health services respectively statutory health insurances) this sum needs to be reduced by the (co-)payments charged to patients, respectively their parents. These vary widely across EU member states. We introduced the simple assumption that for each (adult and paediatric) treatment episode the Third-Party Payer receives a lump sum of €5. For the eight medicines overall net extra cost for the 6-month extension is then estimated at €551m to health systems, or more than half a billion Euros. The co-payments by patients of €38.5m are not accounted for as extra costs, because we assume that they may have taken anyhow these or other medicines for which similar co-payments would have to be paid. This does not hold for one medicinal product. Due to the low price per treatment episode, the full cost of the monopoly rent is allocated solely to patients.

4.3 Benefits derived from cash savings due to ADRs avoided

To estimate potential benefits to health systems from cash savings from avoidable ADRs we assumed that they might be reduced by 20% based on estimates in the literature. They will result from hospital stay and outpatient encounters (emergency room visits and ambulatory services) avoided. For the six-month period, the cumulative estimate across all drugs is for avoidable hospitalisation costs €32,000 and outpatient treatment € 5,000, or overall € 37,000 (over a range of €97 to €31,000 per drug). For 10 years, this sums up to € 741,000. Compared to the overall monopoly rent estimated at more than half a billion Euros, these savings are marginal, leading to benefit-cost ratios of almost zero or a negative return of 99%. Even increasing the estimate for the number of ADEs by another ten times would not lead to any significant results for this item.

4.4 Intangible benefits due to ADRs avoided

In a further step, various non-cash or intangible benefits were estimated. They concern benefits expected from improved actual treatment of children, which result in reduced mortality, improved quality of life (QoL) experiences due to long-term disabilities, and time saved by informal carers. Furthermore, in order to account for further benefits not accounted anywhere else, we add a hypothetical benefit of €10 per each treatment episode. For four medicinal products with very few paediatric treatment episodes compared to all treatment episodes the benefits estimated are considerably higher than for the cash benefits, but still marginal, with less than €100,000 for the 6-month period, and less than €2,000,000 for 10 years. Also the 6-month and 10-year benefit-cost ratios are marginal to negligible. On the other hand, for the product with the largest share of paediatric treatment episodes the estimated value is very different.

It was estimated overall intangible benefits of almost €5m for 6 months, or €100m for ten years. For ten years, we obtained a benefit/cost ratio of 1.5, or a positive rate of return of 50%. For one of the products – the medicine for acute treatment where extra costs accrue only to patients due to higher co-payments, but not to healthcare systems – 10-year intangible benefits are estimated at €80m, leading to a societal benefit/cost ratio of above 5 or a rate of return of more than 400% for this medicinal product. Overall, the greatest benefits are derived from two rather generic and very rough estimates concerning "avoidable reduced quality of life" and a catch-all "additional benefit per paediatric episode" set at €10. The latter term is used as an estimate of a generic benefit for all due to better treatment options (valued at €5); and in addition, to also account for any other significant ADEs (the number of which is unknown) we apply another €5 per episode.

These items are not discussed in the literature, but introduced here to account for any other events and benefits not covered by the earlier items. Intangible benefits for avoidable reduced quality of life are estimated at €2,840,000 across all medicines (range: €6,120 to €2,470,000); for the ten-year period, the estimate is €56,800,000. This value is directly related to the number of paediatric episodes and the estimated number of serious adverse events, where the Asthma medicine far outstrips all others.

Even higher intangible benefits are estimated for the catch-all additional benefit per paediatric episode of €10. Of course, they are directly related to the absolute number of episodes and the percentage of episodes related to paediatrics. Here two drugs are particularly notable: the Asthma medicine with €2,070,000 and the Migraine one with €4,050,000 for 6 months (the range for other medicines is comparably low: €3,200 to €126,500). The sum across all medicines is €6,340,000 for 6 months and €126,800,000 for 10 years. Considering the other intangible benefit estimates cumulated across all drugs, deaths avoided do not contribute to a significant extent to the benefits estimated (€360,000 for 6 months or €7,200,000 for 10 years; only one product is involved); this is due to the low number of reports on death events. For intangible costs to informal carers, the total value across all medicines is €9,400 (with individual values ranging from €22 to €8,000) and €188,000 for ten years.

4.5 Overall benefit-cost ratio estimate for the eight medicinal products

There are two products (Drug A and Drug B) among the eight medicinal products studied here with strongly favourable benefit-cost ratio when calculated over a 10-year period, basically due to non-cash benefits. Drug A is an Asthma pill and provides €32m net benefit, while Drug B, a migraine pill provides €66m net benefit. All other medicinal products have a negative benefit-cost ratio over 10 years. Aggregating cash and non-cash benefits data for all

eight medicinal products, overall benefits of €199m for 10 years are estimated. Overall cash cost to society (patients, health systems) from total monopoly rent to all stakeholders (pharmaceutical industry, wholesalers, pharmacies, governments from value added/sales tax) are estimated at €590m. The overall socio-economic benefit-cost ratio across all medicines is 0.34, the societal overall rate of return minus 66%. A detailed calculation is available in Appendix E of the economic study.

4.6 Estimation of the cost and benefits medicinal products compliant PIPs

The Paediatric Regulation was a first, most important step ("milestone") to improve the onlabel prescribing of medicines for children. However as noted also in other studies, so far only a small start was achieved. As most results from PIPs and other measures are still to come, "however only the children and adolescents of tomorrow" will fully profit. The estimates attempt to cover this perspective for tomorrow by aggregating estimated benefits over a period of ten years.

Furthermore, planning and executing PIPs and other measures, improving labelling and generating more knowledge on the treatment of children are only "one half of the solution". As long as the second half of the solution is not assured, as long as the new knowledge is not translated into adjusted paediatric prescriptions and clinical practice for better healthcare for children, the overall impact will remain small. Knowledge as such may have intellectual, intangible value in satisfying our curiosity, but as long as it is not diffused and applied in paediatric healthcare provision, it does not generate tangible social or economic value. A basic estimate of such potential benefits is estimated. This estimate remains speculative.

Basis of the following data and 'level 2' calculations of benefits and costs is a list of 119 PIPs which passed the compliance check and were approved by EMA as compliant with the requirements for acceptance. From these, the eight medicinal products covered earlier already obtained the extra 6-month SPC extension and are excluded from the following calculations. This leaves us with 111 PIPs relating to medicinal products. Of these, 21 still qualify for such an extension. The remaining 90 PIPs do not qualify or we do not know their status. 3 of these were excluded due to probable double counting because they relate to the same active ingredient (INN), which leaves us with 87 PIPs for consideration.

4.6.1 Characteristics of drugs covered by PIPs

From a comprehensive German study166, it is known that the relative distribution of paediatric prescriptions for the top five therapeutic areas (overall about 35.2 m prescriptions for 2011) in Germany is about as follows:

- Pulmonary/ENT diseases: 60%
- Infectious diseases: 22%
- Central nervous system incl. pain: 17%
- Cardiological/heart diseases: 1%
- Oncology: 0.1%

Classifying the 108 (87 + 21) PIPs according to these areas plus the categories vaccines and others, we obtain the following results:

- Pulmonary/ENT diseases: 7
- Infectious diseases: 15
- Central nervous system incl. pain: 4
- Cardiological/heart diseases: 6
- Oncology: 7
- Vaccines: 13
- Others: 56

"Others" include therapeutic areas like Dermatology, Diagnostics, EndocrinologyGynaecology-Fertility-Metabolism, Gastroenterology-Hepatology, HaematologyHemostaseology, Immunology-Rheumatology-Transplantation, Neonatology-Paediatric Intensive Care, Nutrition, Ophthalmology, Psychiatry, and Uro-Nephrology.

With respect to the type of disease, these can be classified as follows:

- 19 acute
- 9 acute/chronic
- 60 chronic (incl. cancer)
- 13 vaccines
- 7 unknown

Reliable prices for these drugs are difficult to establish.

Table A.30 presents the ranges estimated based on intensive web searches. Mutatis mutandis, it seems that the overall distribution of these PIPs reflects to a great extent the distribution of the eight medicines analysed earlier across these categories.

Table A.30: Price range of medicinal products

Price range	No. of medicinal products
0.01 – 1.00 €	8
1.01 – 5.00€	15
5.01 -10.00 €	9
10.01 € - 50.00 €	20
> 50.00 €	26
Unknown	30

4.6.2 Estimating future benefits and costs

Except for the benefits and costs estimated in the previous section, we do not have any reliable or meaningful estimates at hand. As a very first and speculative estimate, we apply the following logic for estimating benefits. The earlier results have shown that cash benefits are in all probability marginal to negligible, so they are not considered. It should be remembered that the most relevant intangible generic benefit for all paediatric patients due to better treatment options was set at €5, and that in addition, to also account for "significant" ADEs (the number of which is unknown), we applied another €5 per episode.

Therefore, here we only estimate intangible benefits of a generic kind; but we increase the value per paediatric episode from €10 as used in our earlier estimates to a mean value of €15 to also cover in a cursory manner all other intangible benefits as well. Due to the severity of oncology incidents with children, we double the estimated benefit per episode to €30. On the other hand, for vaccines we reduce it to €10 to reflect their overall safety and relatively low ADR incidence rate.

The estimates of the paediatric episodes per drug are derived from the estimates per drug for the eight drugs analysed earlier – taking into account the therapeutic indication, plus setting them into some proportion to the overall relevance of the therapeutic area as indicated by the prescribing figures above for Germany. Details are provided in section 6.3.3 of the economic study.

4.6.3 Estimating costs to health system payers

Estimating overall cash costs to health system payers is similarly difficult and speculative. It is assumed that of the above PIPs only 21 may be granted an additional 6-month SPC. These cover the following therapeutic fields:

- Pulmonary/ENT diseases: 2
- Infectious diseases: 5
- Cardiological/heart diseases: 4
- Oncology: 1
- Vaccines: 1
- Others: 8

Making use of our earlier estimates for the 8 drugs analysed in the preceding section, we set the extra costs resulting from the 6-month monopoly rent of the marketing authorisation holders at a value of about €50m for the first three therapeutic fields covered by 11 PIPs, and at €20m for the other 10. Then we arrive at an overall estimate of 11 x €50m plus 10 x €20m equal to €750m in monopoly costs.

4.6.4 Summary of the results

Comparing these projected first estimates for the 108 extra PIPs, one may contrast the estimated overall intangible benefits of €970m with the estimated extra monopoly costs of €750m. This would lead to a socio-economic benefit-cost ratio of about 1.30 for the 10-year period, or a rate of return of 30% for these additional PIPs. Adding this "surplus" of €220m to the cash and intangible benefits reported in the previous section, our benefit estimate arrives at roughly €500m. This does not fully cover the estimated monopoly cash cost to health systems estimated there at €590m, but improves the overall balance considerably.

4.7 Estimation of R&D spillovers resulting from the PIPs

An estimate of the broader socio-economic benefits results from the private sector investment into paediatric R&D (level 1 analysis) has been conducted. The estimation of R&D spillovers is separate from the estimation of the health benefits achieved in relation to new and improved medicine. The positive spillover effects constitute of additional jobs, growth and innovative activity across (EU and non-EU) sectors that would not have happened if it were not for the R&D investment made in relation to the Paediatric Regulation. The investment in R&D, although a cost imposed to the pharmaceutical industry, can also be viewed as an R&D investment towards new and improved medicine that triggers further investment and growth.

The so-called social rate of return from R&D investment is equal to the sum of the following:

- Private rate of return to the organisation
- The return to the pharma sector, including to generic companies
- The return to other sectors in the economy.

Several studies have estimated rates of return from investment in R&D although the literature in the field of pharmaceutical R&D development is scarce. Annual reporting by GSK (2013, pp. 4 and 2015, p. 4)[2] notes that the estimated internal rate of return of R&D investments is 13% and, in 2013, long-term targets are set at 14%. An earlier study by Garau and Sussex (2007) also refers to a 14% private rate of return.[3] We will use 14% to estimate the private rate of return following € 2,026m investment in R&D (excluding administrative costs) in relation to PIPs.

Estimates of intra-industry and across industry rates of return could not be identified in the literature specifically related to R&D investment in the pharmaceutical industry. One literature review (Health Economics Research Group and RAND, 2008) summarises the rates of return from different types of R&D investment in different sectors and also provides estimates for the rate of return from UK investment in medical research.[4] The study finds that most literature estimates that the total social rate of return from private investment is around 50%, eg 51% as used in Garau and Sussex (2007).

Moreover, the study summarises that the total social rate of return from public investment is at least 20% and could be as high as 67%, with a more conservative best estimate of 30%. Because the R&D spent in relation to the Paediatric Regulation is an imposed investment rather than a strategic company decision, the 30% rate of social return feels more appropriate than the higher rate of return that is associated with private R&D investment. It has been assumed that the intra-industry and across industry rate of return is equal to the difference between the total social rate of return and the private rate of return and amounts to 16%.[5]

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2 https://www.gsk.com/media/2701/annual-report-2013-interactive.pdf and https://www.gsk.com/media/4697/gsk-annual-report-2015.pdf

3 Garau M, Sussex J. Estimating Pharmaceutical Companies' Value to the National Economy. Case study of the British Pharma Group. London: office of Health Economics; 2007.

4 Frontier Economics (2014). Rates of return to investment in science and innovation, A report prepared for the Department for Business, Innovation and Skills (BIS).

5 Because of the method of calculating the intra-industry and across industry rate of return and because we have not 'discounted' the 14% rate of return, the private rate of return may also be overestimated and the intra-industry and across industry rate of return may be overstated.

It should be noted that in the case of spillovers from private investment in R&D, the literature refers to three types of spillovers: improving the productivity of other firms' R&D, encouraging entry of potential competitors, and a reduction of production costs.[6] In the case of the Paediatric Regulation not all three spillovers may be equally present and the spillover effect might be different in relation investment in paediatric-only trials. Overall, knowledge spillovers are likely to contribute to additional growth and investment.

Following the study by the Health Economics Research Group and RAND, the above presented rate of return implies that the R&D investment "implies that for an extra €1 invested in cardiovascular research this year, the UK's GDP will be €0.30 higher next year and every year thereafter, than it otherwise would have been" (pp. 40). Based on this estimate, if all of the €2,103m industry spent in relation to the Paediatric Regulation were to yield a 30% social rate of return that would be equivalent to €608m of GDP every year thereafter.

This degree of perpetuity may be overstated in the case of the Paediatric Regulation and we expect that, in practice, the spillover effect follows a decay curve with an innovation and restructuring phase, following by the diffusion and increase in demand (generics entering the market), and sometime thereafter, a point in time where R&D investment and innovation becomes obsolete. According to a study by Zagame et al (2012), the cumulative effect of an R&D investment can take up to 15 years to accrue but can be preceded by negative rate of return. Following the study, investment benefits from approximately a 10-year period of growth.

For simplicity it has been assumed a linear rate of return with, on average, a total social rate of return of 30% (this is unlikely to be the case and the biggest returns will be experienced in the earlier years) and a maximum cumulative return on investment 10 years after the initial R&D investment. Based on a 30% total social rate of return the total return on investment to society after 10 years amounts to €6,078m and the intra-industry and across industry rate of return after 10 years amounts to €3,242m (see Table A.31).

Considering the 10-year period, both the private and intra-industry and across industry rates of return are larger than the initial investment suggesting a healthy return.

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[6] Health Economics Research Group, Office of Health Economics, RAND Europe. Medical Research: What's it worth? Estimating the economic benefits from medical research in the UK. London: UK Evaluation Forum; 2008.

The economic value of the SPC extension was estimated (extrapolated based on actual data) for 12 products that accrued economic value until 2015 for relevant EU member states to amount to €742k. The estimated social return is significantly higher than this economic value of the SPC extension (excluding cost to society in relation to other products and countries, as well as the dead weight loss in relation to the SPC). Despite the crude methodology used to estimate the effect of spillovers and the challenge to gross up the value of the direct loss to society as a result of the Paediatric Regulation (ie the reward to industry), it suggests that the benefits of the Regulation outweigh the costs.

Table A.31: Estimated return to society and industry of the Paediatric Regulation, millions of euro

Estimated rate of return from € 2,026 investment in R&D	Private rate of return	Intra-industry and across industry rate of return		Total social return	
		From private investment	From public investment (preferred estimate)	From private investment	From public investment (preferred estimate)
After 1 year	€ 284	€ 750	€ 324	€ 1,033	€ 608
After 2 years	€ 567	€ 1,499	€ 648	€ 2,067	€ 1,216
After 5 years	€ 1,418	€ 3,748	€ 1,621	€ 5,166	€ 3,039
After 10 years	€ 2,836	€ 7,496	€ 3,242	€ 10,333	€ 6,078

Estimated total R&D costs of PIPs for the industry per year (2008-2015) was estimated at €2,026m, excluding administrative costs, see Chapter 2.