EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

Health systems, medical products and innovation
Medicines: policy, authorisation and monitoring

COMMISSION REPORT ON THE PAEDIATRIC REGULATION

(ARTICLE 50(3) OF REGULATION (EC) NO 1901/2006)

CONSULTATION DOCUMENT

Deadline for replies: 20 February 2017

This document does not represent the European Commission's official position. It is a tool for exploring the views of interested parties. The statements and conclusions contained in this document do not prejudge the content of the European Commission's future report.

Stakeholders are invited to comment on this consultation paper by 20 February 2017 at the latest. Responses should preferably be sent to sante-pharmaceuticals-B5@ec.europa.eu. They can also be sent by post to Directorate-General for Health and Food Safety, Unit SANTE B/5, BE-1049 Brussels. The subject line of the email or letter should contain the reference '**PCPM/16 — Paediatric Report**'

Commission européenne/Europese Commissie, 1049 Bruxelles/Brussel, BELGIQUE/BELGIË — Tel. +32 22991111

sante-pharmaceuticals-B5@ec.europa.eu

1. ABOUT THE CONSULTATION

1.1. Introduction

The Paediatric Regulation[1] was adopted in 2007 to address a serious gap in knowledge on how medicine should best be used by children. Although evidence-based proof is not disputed for medicine used in adults, this is not the case for medicine used in children. Many products administered to children were prescribed and administered based on experience (off-label) rather than on the results of clinical research.

The Paediatric Regulation **aims to reduce the level of off-label use** and increase the number of medicines specifically developed and tested for children. To do this, it sets up a system of obligations, rewards and incentives, and puts in place measures to ensure that medicines are regularly researched, developed and authorised to meet children's therapeutic needs. It goes beyond the mechanisms set up by the Orphan Regulation,[2] which only provided incentives.

The Regulation obliges companies to agree a paediatric research and development programme ('paediatric investigation plan') with the European Medicines Agency (EMA) for every new product they develop. This will progressively increase the number of products with paediatric indications.

This obligation is complemented by other measures:

- a system of waivers for medicines that are unlikely to benefit children and a system of deferrals in relation to the timing of the paediatric measures to be conducted;
- a reward for complying with the obligation: a six-month extension of the supplementary protection certificate (SPC);
- a specific compliance reward for orphan medicines: an extra two years of market exclusivity added to the existing ten years awarded under the Orphan Regulation;
- a new type of marketing authorisation, the paediatric use marketing authorisation (PUMA), to incentivise the development of paediatric indications for off-patent products;
- a new expert committee, the Paediatric Committee, within the EMA;
- a system of free scientific advice for the industry, provided by the EMA;
- a EU network of networks of investigators and trial centres carrying out paediatric research (Enpr-EMA).

One of the Regulation's undisputed achievements is bringing more attention to **paediatric development**. Companies now consider it an integral part of overall product development.

---

1 OJ L 378, 27.12.2006, p. 1.

2 Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products, OJ L 18, 22.1.2000, p. 1.

In **2013, the Commission published a first report** on the Regulation's impact (Article 50(2) of the Regulation) and stated that there are some promising signs of progress.[3] However, it found that, due to the length of medicinal products' development, it will take at least 10 years to gain a full understanding of the situation.

Under Article 50(3) of the Regulation, in **2017 the Commission must publish a second report**, which should evaluate the Regulation's impact from the perspective of economics and public health. It should also consider whether amendments to the Regulation should be contemplated.

The purpose of this consultation paper is to support the Commission in drafting its second report and to gather stakeholder views and feedback.

1.2. Specific consultation items

The consultation document consists of several statements reflecting on possible lessons learnt from the application of the Paediatric Regulation. These statements are based on the 10-year report to the European Commission prepared by the European Medicines Agency and its Paediatric Committee, an external study on the Regulation's economic impact ordered by the Commission, the experience of the Commission's departments, and reflections on the Paediatric Regulation published in literature and discussed at stakeholder conferences. They do not necessarily represent the Commission's position. Rather, they are a way of further exploring the views of interested parties. Each statement is followed by specific items for consultation (in boxed text); these are the questions on which the Commission seeks the input of interested parties.

1.3. Further background reading

- The Paediatric Regulation (EC) No 1901/2006;
- The 2013 Progress Report of the European Commission;
- 10-year Report to the European Commission — General report on the experience acquired as a result of the application of the Paediatric Regulation as prepared by the European Medicines Agency and its Paediatric Committee.

1.4. How can you contribute?

Stakeholders are invited to comment on this consultation paper, and on the boxed text in particular, by 20 February 2017 at the latest. Responses should preferably be sent to sante-pharmaceuticals-B5@ec.europa.eu. They can also be sent by post to Directorate-General for Health and Food Safety, Unit SANTE B/5, BE-1049 Brussels. The subject line of the letter or email should contain the reference 'PCPM/16 — Paediatric Report'.

When submitting your response, please include your name and e-mail address and specify if you are responding as an individual or as a representative of an organisation. If you represent an organisation, please indicate its name and category (company/business; public authority (local, regional, national, international); NGO; other).

[3] COM(2013) 443 final, http://ec.europa.eu/health/files/paediatrics/2013_com443/paediatric_report-com%282013%29443_en.pdf.

If you represent a company, please state whether it falls within the EU definition of a small and medium-sized enterprise (i.e. less than €50 million annual turnover and fewer than 250 employees).

If your organisation is registered in the Transparency Register, please indicate your **Register ID number** at the beginning of your contribution.

Received contributions will be published online. In view of this, please indicate whether your contribution (choose one option):

(a) Can be published with your personal/organisation information (I consent to publication of all information in my contribution in whole or in part including my name/the name of my organisation, and I declare that nothing within my response is unlawful or would infringe the rights of any third party in a manner that would prevent publication).

(b) Can be published if you/your organisation remain(s) anonymous (I consent to publication of any information in my contribution in whole or in part (which may include quotes or opinions I express) provided that this is done anonymously. I declare that nothing within my response is unlawful or would infringe the rights of any third party in a manner that would prevent publication).

(c) Cannot be published but may be included in statistical data (I understand that my contribution will not be published. My anonymous responses may be included in published statistical data, for example, to show general trends in the response to this consultation).

If you choose option (c), note that your contribution is still subject to requests for public access to documents under Regulation (EC) No 1049/2001.

1.5. What will happen after the consultation?

All contributions will be carefully analysed and inform the report. The final paediatric report will be published in 2017.

2. EXPERIENCE ACQUIRED OVER THE LAST TEN YEARS

2.1. More medicines for children

Figures show that the Paediatric Regulation has had a substantial impact on the development of paediatric medicines in the EU. Pharmaceutical companies now consider paediatric development as an integral part of the overall development of medicinal products, even if some of them continue to perceive paediatric research as regulatory-driven rather than company-driven.

The number of agreed paediatric investigation plans will soon surpass 1 000. In the 2007-2015 period, 99 paediatric investigation plans were completed and over 230 new medicines for use by children (new marketing authorisations and new indications) were authorised, most of them linked to the Paediatric Regulation's requirements. In addition, competent authorities' assessments of paediatric studies undertaken prior to the Paediatric Regulation (Article 45 of the Regulation) have helped collect already known evidence and to complement product information with paediatric data.

A comparison of the situation before and after the Regulation demonstrates a clear positive effect of the Regulation in terms of new authorised medicines. The same is true for international-level comparisons between regions with paediatric-specific legislation and those without: regions with legislative provisions in place have a significantly higher number of new paediatric medicines.

However, it is unlikely that the Paediatric Regulation would ever be able to create a self-sustaining system that could maintain such results without the external support of a specific legal framework for paediatric medicines.

Consultation item No 1: Do you agree that specific legislation supporting the development of paediatric medicines is necessary to guarantee evidence-based paediatric medicines?

2.2. Mirroring paediatric needs

The starting point for most paediatric investigation plans is a research & development programme for adults. Under Articles 7 and 8 of the Paediatric Regulation, adult developments have to be screened for their potential use in children. A consequence of this approach is that progress in paediatric medicines is dependent on companies' adult product pipeline, i.e. on advances in the therapeutic areas and conditions in which there is a need or a market in the adult population. Where the adult needs overlap with paediatric needs, children will benefit directly. However, there is a considerable number of diseases that are biologically different in adults and children, where the disease burden differs, or that only exist in children.

Achievements of the Paediatric Regulation are therefore not the same across all therapeutic areas, even if agreed paediatric investigation plans cover a large variety of conditions. Some therapeutic areas have seen considerable progress over the past ten years, while for others the availability of new therapies is limited or has not yet materialised. It could be argued that the qualitative effect of the Paediatric Regulation does not really differ from other statutory instruments, which intend to redirect private investment towards previously neglected areas, such as for example the EU legislation on

rare diseases.[4] They are an important enabler, but as far as their effect is concerned, they are partly dependant on factors that can hardly be influenced by legislation.

Consultation item No 2: Do you have any comments on the above? To what extent and in which therapeutic areas has the Regulation contributed to the availability of important new treatment options?

2.3. Availability of paediatric medicines in the EU

The Regulation includes several instruments to ensure that, once a paediatric investigation plan is completed and the paediatric medicine is authorised, the product is placed on the market and available in the entire EU. For example, the SPC reward under Article 36 will only be granted if the product is authorised in all Member States. Moreover, Article 33 contains an obligation to place the product on the market within two years of the date on which a new paediatric indication is authorised.

These are complementary measures to ensure the availability of new paediatric medicines to all patients in the EU and to allow physicians and clinicians to use them in their daily work. At the same time, certain inertia in the system is reported, where physicians may not immediately switch treatment habits to newly authorised products.

Consultation item No 3: In your experience, has the number of new paediatric medicines available in Member States substantially increased? Have existing treatments been replaced by new licensed treatments?

2.4. Reasonable costs

The Paediatric Regulation places an additional burden on pharmaceutical companies by requesting them to carry out additional paediatric research which they might not have undertaken otherwise.

An evaluation of paediatric investigation plans agreed over the last ten years, based on an external study ordered by the European Commission, shows that the total R&D costs per plan on average amount to € 18.9 million, with each plan including an average of three clinical studies. On top of this, companies incur administrative costs of around € 720 000 in relation to filing of the initial submission of a paediatric investigation plan and for subsequent modifications. In total, the estimated average incurred costs per paediatric investigation plan is therefore just below € 20 million. Based on the average number of new plans agreed per year (107 in 2008-2015), this amounts to total annual costs of € 2.1 billion incurred by the industry. At the same time, this may be an overestimate given that not all agreed paediatric investigation plans will be completed as some are discontinued, for example if the company decides to shelve the adult development programme.

The above figures suggest that the additional costs incurred by industry as a consequence of the Paediatric Regulation are reasonable and that they lead to only a limited increase in the total costs of medicine development[5].

---

[4] Regulation (EC) No 141/2000 on orphan medicinal products, OJ L 18, 22.10.2000, p.1.

[5] These average costs for paediatric trials are only a small fraction of the cost estimates typically published for new investigational compounds covering the overall (adult) development.

Consultation item No 4: Do you have any comments on the costs for pharmaceutical companies to comply with an agreed paediatric investigation plan?

2.5. Functioning reward system

The objective of the reward system introduced by the Paediatric Regulation (6-month SPC prolongation or orphan-specific reward) is to allow companies to recuperate the additional costs incurred as a result of the Paediatric Regulation through prolonged protection periods.

An analysis of the paediatric investigation plans completed so far shows that not all companies were able to obtain a reward. Figures show that at least 55 % of the completed plans benefitted from a reward, however. Most rewards took the form of a prolongation of the SPC certificate; in a few cases (four), the market exclusivity period of an orphan medicinal product was extended. In several instances, companies waived the product's orphan status shortly before marketing authorisation in order to make the product eligible for the SPC reward rather than the orphan reward, as the former is often considered to be economically more attractive.

There are various reasons for why not all completed paediatric investigation plans benefitted from a reward. In some cases, companies were not able to complete the paediatric development before the deadline for submitting a request to prolong the SPC expired (two years in advance). In others, products that fell under the scope of Article 7 of the Paediatric Regulation were not protected by a patent and/or SPC and were therefore not eligible for a reward despite being subject to the obligations.[6] It is however, expected that over time the ratio of products that benefit from a reward will increase, as companies start to plan better and earlier to complete more paediatric investigation plans before the SPC expires.

Another factor that complicates the reward system is linked to the fact that SPCs have to be obtained from the national patent office in each Member State in which an SPC exists. However, the number of SPC prolongations granted in the last ten years (nearly 500) shows that companies regularly receive the reward from the national patent office in which they apply.

The monetary value of the SPC reward depends largely on the overall revenue that a particular product brings in during the period in which it is protected by an SPC. Typically, this period corresponds with the peak in sales. In most cases, the reward's value is likely to surpass the average paediatric investigation plan compliance costs discussed under point 2.4, in some cases significantly. However, this surplus may be used to cover the costs of discontinued paediatric investigation plans or ones that did not receive a reward.[7]

Consultation item No 5: Do you agree that the reward system generally functions well and that early, strategic planning will usually ensure that a company receives a reward?

---

[6] With its judgement on a 'negative term' SPC in case C-125/10 (ECLI:EU:C:2011:812), the Court of Justice increased the value of the SPC reward.

[7] Current figures suggest that around 20 % of agreed paediatric investigation plans are discontinued. This figure is well below the normal attrition rate for product development between end-of-phase I studies and phase III studies.

2.6. The orphan reward

When the legal proposal for the Paediatric Regulation was discussed, about 60 % of orphan-designated products were off-patent. This was the beginning of the implementation of the Orphan Regulation, and a few of older substances had been transformed into pharmaceutical quality-medicinal products. This was one of the reasons for why the legislature decided to introduce an orphan-specific reward in the Paediatric Regulation, in the form of a two-year extension of market exclusivity.

However, currently, more than 90 % of newly authorised orphan medicines are on-patent. The SPC reward may be economically more attractive for them, but orphan-designated products are only eligible for the orphan reward (Article 37).

In some instances, especially for medicines that have both common and rare conditions, companies voluntarily waived the orphan designation in order to make the product eligible for the SPC reward. This can be considered as 'playing the system' or as showing that the orphan reward has only a limited impact. At the same time, however, most of the products that received the orphan reward belong to the category of 'orphan blockbusters', i.e. they generate substantial revenue in a niche market for the companies concerned.

Consultation item No 6: How do you judge the importance of the orphan reward compared to the SPC reward?

2.7. Improved implementation

The Paediatric Regulation gives the EMA and its Paediatric Committee primary responsibility for handling paediatric investigation plans, deferrals and waivers. Hence, the EMA plays a key role in the Regulation's implementation. Efforts have been made to learn from the first years of implementation and to simplify paediatric investigation plan opinions to reduce the need for modification if there are non-significant changes to the paediatric investigation plan programme. These efforts have helped to decrease the overall ratio of changes to paediatric investigation plans.

Additionally, the revision of the Commission's guidelines on the format and content of paediatric investigation plans in September 2014[8] introduced measures to streamline the process of agreeing the plans. Moreover, in 2015 the EMA introduced early interaction meetings with companies to encourage them to consider paediatric needs in the early phases of medicine development. These early meetings also make it possible to determine the appropriate timing, and integration of paediatric measures in the context of the overall medicine development.

To facilitate paediatric development across regions, in 2013 the EMA and its US counterpart the FDA launched so-called 'common commentaries' on paediatric development plans that have been submitted to both the EMA and FDA and that must are therefore be reviewed by both agencies. While informal and non-binding, these commentaries and discussions between the two agencies have helped to align views and to avoid contradictory requirements with regard to the paediatric development programme.

[8] Guideline on the format and content of applications for agreement or modification of a paediatric investigation plan, OJ C 338, 27.9.2014, p. 1.

However, it remains a challenge for the EMA and its Paediatric Committee, as well as for companies, to consider key aspects of medicine development when certain information is not yet known and when discussions are still based on assumptions and scarce data. This is true especially as one of the objectives of paediatric development plans is to create legal certainty about regulatory authorities' expectations towards companies. On the other hand, only early interaction makes it possible for paediatric development to be seamlessly integrated into overall product development instead of being an afterthought. In principle, it should also lead to more (cost-)efficient R&D, as it makes it possible to consider integrating adolescents into adult trials thereby reducing overall study costs.

Consultation item No 7: Do you agree that the Regulation's implementation has improved over time and that some early problems have been solved?

2.8. Waivers and the 'mechanism of action' principle

The Paediatric Regulation establishes a system which waives the requirement of a paediatric research programme for specific products or for classes of products (Article 11). This happens if a product is likely to be ineffective or unsafe for children or if it does not have a significant therapeutic benefit over existing treatments. The obligation is also waived if the disease or condition for which the product is intended occurs only in adults.

The waiver aims to avoid unnecessary research and to correctly frame the scope of the obligations. However, as simple and straightforward as the waiver concept seems to be, it has been criticised over its effects, especially in cases where the obligation is waived because the adult disease does not exist in children. One particular example is paediatric oncology, where many paediatric cancers share biological similarities with adult cancers, but occur in different organs and therefore are usually considered as different conditions. Consequently, a company may be entitled to a waiver even if the mechanism of action of the adult product under development may potentially also be effective in treating certain paediatric cancers.

This has led to missed opportunities in the past, even though some companies decided not to apply the waiver and to carry out paediatric research on a voluntary basis and based on the 'mechanism of action' principle. These companies understood that doing so would make them eligible for a reward under the Paediatric Regulation, so the voluntary research serves not only a public health purpose, but may also prove economically beneficial to them. The EMA's 2015 review of class waiver decisions may help to engage in a dialogue with applicants regarding voluntary research. However, some parties consider that the voluntary approach will fall short and advocate for a stronger reliance on the 'mechanism of action' principle. Others argue that changes to the waiver concept risk endangering the objective of disease-agnostic statutory rules as well as the predictability of paediatric investigation plan decisions with regard to the expected scope of paediatric research.

Consultation item No 8: Do you have any comments on the above? Can you quantify and qualify missed opportunities in specific therapeutic areas in the last ten years?

2.9. Deferrals

The Paediatric Regulation includes provisions for deferring the initiation or completion of some or all measures contained in a paediatric investigation plan (Article 20), with a

view to ensuring that research is carried out only when safe and ethical. It also includes measures to avoid that the requirement of completing a paediatric investigation plan blocks or delays the authorisation of adult products. Experience shows that deferral is a widely used instrument and there is no evidence that the paediatric requirements have delayed the processing of adult application, with the exception of those rare cases where companies submitted the paediatric investigation plan late, i.e. only shortly before they planned to submit the adult application.

The concept of deferral is in some instances also useful to delay the initiation of a paediatric trial until further information from adult trials is available, especially regarding the safety of potentially toxic compounds. At the same time, deferrals that delay the initiation of the paediatric trial until after the adult authorisation can create problems, as in these instances recruitment for paediatric studies can become more difficult once the product is available on the market. Parents often fail to see the added value of agreeing that their child participates in clinical research if the adult product can already be used (off-label) in children.

Extensive deferrals may also cause frustration among clinicians and patients, especially if they mean that the paediatric product to treat a life-threatening disease will only be available to children years after the adult authorisation comes through. Moreover, long deferrals may undermine the enforceability of paediatric requirements, and the availability of the reward, especially if the deferral ends after protection periods for the product have expired.

Consultation item No 9: Do you agree with the above assessment of deferrals?

2.10. Voluntary paediatric investigation plans

The EU was not the first region to introduce specific legislation in order to tackle the absence of medicines that are tested and authorised for use by children. In fact, the United States passed paediatric-specific legislation already in 1997. While the general goal is similar, there are certain differences in scope and nature. For example, with the so-called 'written request' US legislation includes an instrument that allows its Food and Drug Administration to submit to companies a paediatric research proposal, which, if honoured, makes the company eligible for an incentive.

Some argue that EU legislation lacks the tools to invite and incentivise companies to voluntarily carry out paediatric research in the form of a voluntary paediatric investigation plan. However, although the Paediatric Regulation is geared towards obligations, it also includes the possibility to submit *voluntary* paediatric investigation plans. Nothing prevents a company from submitting a paediatric investigation plan request for a paediatric-only development or to complement an adult development with a paediatric investigation plan, even if it is entitled to a waiver (under Article 11(1)(b)). In these circumstances, the company in question is able to benefit from rewards under the Regulation and these serve as an incentive. Some companies fully realise the potential of voluntary paediatric investigation plans and consider paediatric research projects beyond the obligations of the Paediatric Regulation, while others are less forthcoming.

Consultation item No 10: Do you have any comments on the above?

2.11. Biosimilars

Under Article 9 of the Paediatric Regulation, certain product categories are exempt from the obligations introduced. This is for example the case for generic medicines and biosimilars and is justified by the fact that the relevant knowledge for using the active substance in children was already obtained through clinical research with the originator product (at least, for those products which were authorised after the Regulation entered into application). It is therefore not justified to repeat paediatric trials for these product categories.

At the same time, some originator products are authorised with specific age-appropriate paediatric formulations. Some argue that biosimilars copying the originator product may not necessarily include these paediatric formulations, which may lead to products entering the market without being adapted to paediatric use. This could potentially exclude children from benefitting from these products. At the same time, in the case of biosimilars, it is likely that the originator product will remain on the market despite direct competition from biosimilars. A product that is adapted for use in children will therefore remain available.

Moreover, if the company holding the marketing authorisation for the originator product would intend to discontinue marketing the product, it may be obliged to transfer the marketing authorisation to a third party in accordance with Article 35 of the Regulation. This rule was introduced to ensure that important paediatric products do not disappear once regulatory protection periods and patent protection expire.

Consultation item No 11: Do you have any comments on the above?

2.12. PUMA — Paediatric-use marketing authorisation

The paediatric-use marketing authorisation (PUMA) introduces an incentive to carry out research into the potential paediatric use of off-patent medicinal products that have been authorised for adults. The main goal of the PUMA concept is to stimulate research in existing products and to help transform known off-label use into authorised use that is safer and better circumscribed.

To date, only three PUMAs have been authorised, which is disappointing. The PUMA concept struggles with similar problems as any scheme meant to encourage companies to invest in additional research for known compounds that have been available on the market for decades. Medicine developers fear that a PUMA will not necessarily prevent physicians from continuing to use competitor products with the same active ingredient off-label, at lower costs, nor substitution for cheaper forms at the level of pharmacies. Moreover, national health care payers are often hesitant to agree to a premium price for such products. These are complex factors that can hardly be addressed at EU level, through the Paediatric Regulation. They concern downstream decision-making at national level, which is outside the scope of EU law.

In 2014, the Commission and the EMA clarified that a paediatric investigation plan for a PUMA does not have to necessarily address all age groups. However, this measure does not seem to have stimulated interest. This being said, in the case of rare diseases orphan marketing authorisations may have been chosen over PUMAs.

It is often argued that the PUMA concept would require additional funding from public sources. However, the Commission provided funding for off-patent medicines projects for several years and only some of these projects led to an authorised product.

Consultation item No 12: Do you share the view that the PUMA concept is a disappointment? What is the advantage of maintaining it? Could the development of off-patent medicines for paediatric use be further stimulated?

2.13. Scientifically valid and ethically sound — Clinical trials with children

The Paediatric Regulation aims to ensure that evidence of the quality, safety and efficacy of medicinal products is generated before the product is used by children. This means more clinical research carried out with children prior to authorising medicines. However, so far the exact impact on the number of paediatric trials and study participants is difficult to quantify due to some shortcomings in the available databases with regard to mandatory data.

Generally speaking, EU legislation is well equipped to ensure that paediatric research is scientifically valid and ethically sound. These aspects are considered not only by the EMA's Paediatric Committee in its assessment of paediatric investigation plans, but also by the ethics committees and regulatory authorities that are responsible for authorising individual clinical trials. It is important that everything possible is done to make sure that the specific vulnerability of child patients is fully considered and that the children's best interests are taken into account.

The Regulation has fostered and stimulated expert discussion about the optimal design of paediatric trials. This includes initiatives related to the exchange of good practices, development of new scientific guidelines, and modelling and simulation, with the aim of reducing the number of necessary study participants. Additionally, it brought attention to the debate about the role that children should play in research decisions and about the proper protection of children taking part in research. Initiatives range from the creation of young people advisory groups to discussion of appropriate information about clinical studies for patients and parents, to practical issues, such as forms and other paperwork.

Still, paediatric trials pose particular challenges. For example, recruitment difficulties frequently lead to delays in conducting and completing them. Paediatric trials also tend to be multi-centre trials, sometimes with just a few patients per site, which can create operational challenges, including with maintaining the necessary staff and expertise on-site.

Moreover, sometimes there are waves of development, with a peak in activities carried out by multiple companies in parallel, for the same adult disease. A recent example is type II diabetes. Such waves lead to an increase in paediatric research programmes, even if — when seen from the perspective of therapeutic needs — not all of them would have been necessary. They may also lead to feasibility problems with regard to the conducting of trials, as companies may target the same patients and the same sites around the same time. The EMA and its Paediatric Committee have made efforts to alleviate the problem by trying to convince stakeholders to engage in collaborative research, but experience shows that companies are hesitant to engage in this way, as they are not used to collaborative projects for new developments, especially if they may potentially reach blockbuster status in adults.

Consultation item No 13: Do you have any comments on developments in clinical trials with children following the adoption of the Regulation and in view of the above discussion?

2.14. The question of financial sustainability

Implementation of the Paediatric Regulation presupposes a significant investment (of resources) by Member States, e.g. by appointing members to the Paediatric Committee and by contributing to the assessment of paediatric investigation plans and providing free-of-charge paediatric scientific advice, thereby supporting the activities of the EMA.

As the assessment of paediatric investigation plans does not involve any fees, the EMA does not reimburse national experts for doing this work. There are some concerns that this could potentially have a long-term impact on the proper functioning of the system.

Consultation item No 14: Do you have any views on the above and the fact that the paediatric investigation plan process is currently exempt from the fee system?

2.15. Positive impact on paediatric research in Europe

The Paediatric Regulation has had a positive effect on paediatric research. It is however, recognised that such research is geared towards product development. For some diseases or therapeutic areas, a good understanding of the underlying disease is still lacking. Additional basic research on the diseases themselves would therefore be beneficial to facilitate and inform appropriate product development. This cannot be guaranteed through the Regulation, but requires additional efforts and funding from public and private sources.

In addition, the Regulation is generally beneficial for research infrastructure due to the increase in research projects that intend to comply with paediatric investigation plans. This includes a positive spill-over effect in terms of additional jobs, growth and innovative activity across the EU that would not have happened if it were not for the R&D investment made in relation to the Regulation.

In anticipation of an increase in paediatric trials, several Member States have increased the capabilities of existing research networks or have established networks specifically dedicated to paediatric medicines. In addition, the European Network for Paediatric Research at the EMA (Enpr-EMA) was established in 2009 as a ‘network of networks’ to provide efficient inter-network and stakeholder collaboration. To date, nearly 40 networks are part of Enpr-EMA and share good practices on common quality standards.

Despite these recognised efforts in recent years, the paediatric research infrastructure needed to conduct paediatric studies did not develop at the same pace to meet the growing need and to ensure consistent long-term availability beyond single trials. This is one of the reasons for why the IMI public-private partnership (‘innovative medicines initiative’) is currently considering to facilitate the establishment of an EU paediatric clinical trial network.

Consultation item No 15: How do you judge the effects of the Paediatric Regulation on paediatric research?

2.16. "Mirror, mirror on the wall" - Emerging trends and the future of paediatric medicines

The way pharmaceuticals are developed may change over time due to scientific advances and technological developments. For example, small chemical molecules dominated the market for authorised medicines for a long time, while in recent years there has been an increasing shift towards large, biological molecules.

Other trends include the stratified development of medicines (adaptive pathways) or the concept of personalised medicine (or 'precision medicine'), which aims to optimise the use of medicines by targeting them to patients' individual genes to ensure that they will be truly responsive to treatments.

These new (emerging) development paradigms may be perfectly compatible with the mechanism introduced by the Paediatric Regulation. At the same time, however, it cannot be neglected that the Regulation was developed at a time when the traditional, classical way of pharmaceutical development was still pre-dominant; hence the idea of linking the obligations introduced under the Regulation to broad adult medicine development.

Furthermore, the Paediatric Regulation builds on pharmacological differences between patients based on age. However, concepts such as precision medicine may have the effect of prioritising other distinguishing features in the future, potentially rendering age less relevant. In order to ensure the continued relevance and impact of the Paediatric Regulation it is therefore important to understand the extent of such future trends and their effect on paediatric medicines.

At the same time, it is important to ensure that children fully benefit from new emerging concepts, such as for example precision medicine.

Consultation item No 16: Are there any emerging trends that may have an impact on the development of paediatric medicines and the relevance of the Paediatric Regulation?

2.17. Other issues to be considered

The Paediatric Regulation has to be seen in the context of other EU legislation regulating and encouraging the development of medicines. For example, as far as rare diseases are concerned, the objective of stimulating research and development is also fostered by Regulation No 141/2000 on orphan medicinal products. The complementary effect of those instruments may need to be considered.[9]

Consultation item No 17: Overall, does the Regulation's implementation reflect your initial understanding/expectations of this piece of legislation? If not, please explain. Are there any other issues to be considered?

[9] See also Council conclusions on strengthening the balance in the pharmaceutical systems in the EU and its Member States from June 2016.