European Federation of Pharmaceutical Industries and Associations

Draft ☐ Final ✱

# COMMISSION REPORT ON THE PAEDIATRIC REGULATION[1]

EFPIA's answer to the Commission's Consultation Document

**Author:** EFPIA ✱ **Date:** 16/02/2017 ✱ **Version:** FINAL




✱ **EFPIA's answer**

## About EFPIA

The European Federation of Pharmaceutical Industries and Associations (EFPIA) represents the pharmaceutical industry operating in Europe. Through its direct membership of 33 national associations and 42 leading pharmaceutical companies, EFPIA is the voice on the EU scene of 1,900 companies committed to researching, developing and bringing to patients new medicines that will improve health and the quality of life around the world.

**Transparency Register number:** 38526121292-88

## Introduction

The Paediatric Regulation has contributed to the improvement of child health in Europe by stimulating the development of drugs suitable for children and the building up of significant paediatric-specific expertise. The Regulation has promoted and been successful in building a holistic approach to paediatric research, which has become an integral part of companies' development programs.

Significant progress has already been accomplished up to this point, demonstrating the effectiveness of the Regulation to stimulate and improve the quality of paediatric research and development. However, because of the long development cycle of new paediatric medicines, the full impact of the Regulation on the availability of paediatric medicines is not yet fully apparent. A significant number of Paediatric Investigation Plans (PIPs) are on-going and will deliver additional results in the coming years. This progress should be reinforced and built on, rather than disrupted.

EFPIA believes that the implementation of the Paediatric Regulation can be further improved through pragmatic measures, building on all stakeholders' experience and the lessons learned, to better promote

[1] Article 50(3) of Regulation (EC) No 1901/2006
[2] EMA's 10-year Report to the European Commission on the experience acquired as a result of the application of the

and optimise paediatric research and medicines development in Europe, to the benefit of young patients and society as a whole.

In particular, EFPIA members propose the following:

1. **A comprehensive inventory of disease-based unmet paediatric needs, based on the existing requirements of Article 43 of the Paediatric Regulation,** to indicate clearly for each need if there is research on-going and if so, what type of research, ensuring visibility to all stakeholders of areas where research is most needed and avoiding that the paediatric population is subjected to unnecessary or unfeasible clinical trials. It should include, specifically for paediatric oncology needs, references to scientific publications on tumour target identification and validation that support a particular oncology need. Multiple stakeholders (industry, regulators, epidemiologists, patient groups, paediatric networks) should be involved in this assessment for review by the Paediatric Committee (PDCO).

2. **Revising EMA policy on the determination of the conditions for a PIP/waiver** to ensure a clear and predictable understanding of the references framing the discussion for potential paediatric development plans, particularly in the field of oncology. This Policy already allows a Mechanism-of-Action (MOA) approach, and the proposal is to further refine it in conjunction with the inventory described above. In their discussion on whether to request a full PIP or to grant a waiver, PDCO (and companies) would use the inventory to identify the area of unmet need to focus on, based on the adult condition; for oncology products, if the adult condition is not a suitable basis for the PIP, the MOA should be used to identify the most plausible, validated paediatric cancer target with an unmet need. In all cases, the discussion should also take into account the feasibility of the trial(s).

3. **Improving the efficiency of PIPs through earlier and better scientific and regulatory dialogue, without changing the timing of PIP submission.** This should be done with an extended expert base, to agree on the overall development plan, taking into account the level of evidence available at the point of interaction. Patients, their families and/or representatives should be included when feasible as part of this extended expert base in order to include their perspective (for example, their perspective on the practicality/desirability of certain trial designs). This would allow the creation, agreement on and conduct of the PIP to fit more naturally within the drug development process, improving the scientific credibility of the PIP and reducing the need for multiple modifications, offering greater certainty to all that the agreed PIPs can be effectively completed.

Furthermore, as most paediatric product development is carried out globally, a globally **aligned approach** to the important elements of a paediatric development program would be a major step towards enhancing efficiency of paediatric drug development, reducing unnecessary clinical trials in children and helping to ensure that children have faster access to new medicines.

Finally, EFPIA would encourage the Commission to use more outcomes-oriented metrics in assessing the Regulation, focusing on the impact of the Regulation in improving health outcomes for paediatric patients. This is critical to better understanding the performance of the Regulation.

EFPIA is willing and committed to working with all stakeholders to find solutions to progress further toward improving children health in Europe. Regular stakeholder interactions are necessary for that purpose.

## Table of contents

# 1. More medicines for children

**Do you agree that specific legislation supporting the development of paediatric medicines is necessary to guarantee evidence-based paediatric medicines?**

EFPIA agrees that the Paediatric Regulation has had a substantial and positive impact on the development of evidence-based paediatric medicines in the EU, as concluded in the EMA's 10-year report to the European Commission[2] and noted in the recent European Parliament Resolution[3]. It has resulted in more treatments being authorised for children and more information becoming available for prescribers and patients on the paediatric use of medicines.

Paediatric development is now integrated into the overall development of medicinal products and companies' expertise in this area of research has grown considerably and continues to increase. Many companies have established dedicated internal and/or external paediatric advisory teams that are consulted during development to ensure that necessary expertise is provided, and to transfer key learnings across other development programs. Likewise the experience and expertise of other stakeholders, including the EMA itself, has grown and great progress has been made in terms of the regulatory approach and implementation of the Regulation in practice. The Regulation has also encouraged the establishment of new patient organisations, and the development of multi-stakeholder networks, dedicated to the search for new therapies for children. As such, the Regulation provides the foundation for the further development of scientific guidance, broader exchange of experience, support from important institutions such as ethics committees, and an increase in the general public awareness of the importance of paediatric research.

EFPIA also agrees that the data for the EU, and in comparison with other jurisdictions, indicate that this impact is not achieved without legislation, and therefore a legal framework for paediatric research and development is appropriate. Nevertheless, the development of evidence-based paediatric medicines was already being undertaken by our member companies prior to the introduction of the Paediatric Regulation and such development, outside the scope of the Regulation, continues today. In this regard we would particularly note the vaccines that have been developed for childhood immunisation, which has long been one of the most successful and cost-effective measures for improving public health, protecting the paediatric population against a multitude of diseases.

EFPIA believes that the Regulation is delivering on its objectives and this is a long term, continuous process. The timelines for individual development programmes are necessarily lengthy and the challenges inherent in this paediatric research are great, but the large number of on-going PIPs will continue to produce still more positive results over time. More work is undoubtedly required to improve the efficiency and speed of paediatric medicines development, and EFPIA believes that this is a very practical, rather than legislative, issue and a lot can be achieved in the relatively short term by pragmatic measures to optimise the implementation of the Regulation, rather than requiring new legislation.

[2] EMA's 10-year Report to the European Commission on the experience acquired as a result of the application of the Paediatric Regulation, 27.10.2016, available here.
[3] Motion for a Resolution on the Regulation on Paediatric Medicines, 2016/2902(RSP), 15.12.2016, available here (to be updated as final edition available).

## 2. Mirroring paediatric needs

**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?**

All stakeholders need to have a broader look at what is inhibiting paediatric medicine development in some areas. Progress in paediatric medicine is dependent first on foundational medical research, which is still very limited in many instances, and second on companies' product pipeline and it is therefore understandable that achievements vary across therapeutic areas.

EFPIA agrees with the European Commission that legislation can be an enabler. Other factors also play an important role, in particular scientific plausibility. This can be illustrated with the example given in the EMA's 10-year report of the new treatments that have been developed for the rare paediatric rheumatic disease Juvenile Idiopathic Arthritis[4]. These developments are largely driven by advances in the understanding of the pathology of the disease and on advances in the development and manufacture of targeted biological substances, and the Paediatric Regulation has mainly been an enabler.

For research and development to be better aligned with paediatric needs, these needs must be clearly defined. EFPIA notes that the Regulation foresees an inventory that 'will highlight the therapeutic needs of the paediatric population so that companies can identify opportunities' (Article 43). The current implementation of this Article is drug- rather than disease-centric, and therefore fails to provide both industry and academia with a clear picture of the therapeutic and prophylactic needs in the paediatric population.

EFPIA therefore recommends that the way Article 43 has been implemented is revisited in line with what the legislation requires. Agreeing on an inventory of paediatric needs requires a multi-stakeholder dialogue of regulators with patients, their families, healthcare professionals (HCPs), academia and industry. Once in place, the inventory will enable science-based paediatric research and development that focuses on areas of unmet need, and help limit further research in areas where satisfactory treatment(s) have already been researched or approved.

Research in paediatric medicine is not only done by industry. Public funding, including EU support and funding from Horizon 2020 and the Innovative Medicines Initiative (IMI), a joint undertaking between the European Union and the pharmaceutical industry, should be directed to further foundational research into paediatric diseases, methodology development and clinical research infrastructure and networks to enable smooth development of future medicines and better outcomes[5].

[4] EMA's 10-year Report, *op. cit.*, p. 31

[5] Please see 'Public- and Private-Sector Contributions to the Research and Development of the Most Transformational Drugs in the Past 25 Years: From Theory to Therapy' DIA Therapeutic Innovation & Regulatory Science 2016, Vol. 50(6), S. 759-768 which details the contribution of academia and pharmaceutical industry to basic research and development.

## 3. Availability of paediatric medicines in the EU

**In your experience, has the number of new paediatric medicines available in Member States substantially increased?**

EFPIA agrees there has been an increase in the number of new paediatric treatments authorised following the implementation of the Paediatric Regulation in 2006. This is presented in the EMA's 10-year report which showed for instance that 68 new medicines and new indications were centrally authorised for paediatric use between 2012-2014, compared with only 31 between 2004-2006; the number of authorised products with a new paediatric posology increased from 21 in 2004-2006 to 35 in 2012-2014[6].

However, regulatory authorisation does not automatically equate with availability in a EU Member State. Whilst the information in the Summary of Product Characteristics (SmPC) will be updated following completion of the paediatric investigation plan (through the addition of a paediatric indication and/or inclusion of the results of paediatric studies, both positive and negative), accessibility and further arrangements for placing on the market will have to be agreed in each Member State. In some cases, national HTA or reimbursement bodies will request different and additional evidence from that required by the regulators, which may impact availability of medicines for patients. The availability of medicines to all patients, including children, is an important issue, and EFPIA supports multiple stakeholder engagement in this process to ensure the most efficient approach.

The decision to prescribe a newly available paediatric medicine primarily lies with the Healthcare Professional (HCP) and their judgment as to the best approach for an individual patient. HCP awareness of new paediatric medicines, and likely use, tends to be greater in specialist paediatric centres. However, EFPIA believes that HCPs are best placed to make treatment decisions and supports the provision of clear information regarding newly authorised and available paediatric medicines by the EU Member States agencies to HCPs, using appropriate national tools and systems, in order to assist them in their decisions and direct them towards appropriate use of medicines within their authorised indications.

The Paediatric Regulation is considered to be one corner stone in the overall system. Alignment and mutual agreement of all stakeholders, including at national level, is needed to achieve the overarching goal of making innovative treatment options available to children.

## 4. Reasonable costs

**Do you have any comments on the costs for pharmaceutical companies to comply with an agreed paediatric investigation plan?**

EFPIA is willing to contribute constructively to the evaluation of the legislation but believes it is not relevant to look at development costs on a product-by-product basis. Rather, the analysis should focus on the broad impact and benefits stemming from the implementation of the Regulation.

As noted in the consultation document, the Paediatric Regulation requires companies to carry out paediatric development programmes, in agreement with the PIP terms. This obviously comes at a cost, which is however difficult to assess.

[6] EMA's 10-year Report, *op. cit.*, p. 12

When the Paediatric Regulation was adopted, it was accompanied by extensive analyses on the expected impact, predicting the value to children and society, the value and cost to pharmaceutical companies for complying and the costs to regulators and health systems for implementing the Regulation. These analyses anticipated that the administrative, research and development costs would vary significantly across the spectrum of medicines.

In 2004, the preliminary Extended Impact Assessment of the draft Paediatric Regulation conducted by RAND Europe indicated that "the plan and the associated clinical trials [would] raise the costs involved in applying for a marketing authorisation by between €1 and €7 million per drug for phase III clinical trials in children for an average of €4 million".

While more recent estimates indicate that actual costs of complying with the Regulation turned out to be much higher than predicted, reflecting the largely unforeseen complexity of implementing the Regulation, they have also highlighted the difficulties associated with, first, collecting consistent information and second, drawing meaningful conclusions on the costs of companies' conduct of an agreed PIP in compliance with the Regulation. Difficulties were encountered in precisely assessing and comparing the various types of costs across complex organisations and research programmes, where internal structures and accounting practices do not lend themselves to making calculations that specifically separate paediatric research from other research and related activities.

Ultimately, each PIP is unique and it is clear that these costs vary significantly, subject to many factors. The costs of complying with the Regulation vary according to the therapeutic area, the product being studied, the number of indications and therefore PIPs by product, the scope and content of the PIP(s), including the number of studies to be conducted or the number of patients enrolled in trials, whether the product is developed for a paediatric population only or together with an adult indication, whether the PIP associated pivotal study was completed or terminated early and how long it took to complete. Also, developing paediatric formulations / presentations can be a very challenging, lengthy and costly process.

In particular, the additional costs may be significant in the case of prophylactic vaccines which target a healthy population and for which a larger clinical safety database is expected before and after the grant of the marketing authorisation by the authorities. Also, for certain diseases the incidence rate may be low in the paediatric population or the disease may only occur in a certain segment of the paediatric population. In order to enrol sufficient number of subjects, paediatric clinical studies for vaccines may have to be conducted for several years and in a large number of investigational centres worldwide.

The relative costs of complying with a PIP will further vary depending on the size of the company and the number of PIPs it is conducting. Duplication of trials due to EMA's and FDA's different requirements may further add to these costs – it can take years to reach agreement with the EMA and FDA on a PIP/PSP. As a result, EFPIA finds it difficult to rely on averages that can neither be representative nor meaningful, all the more since they are based on necessarily limited samples.

Current cost estimates also do not take into account e.g.:

- Additional clinical trials in adults that may be required to safely administer a new dosage form in children and may also be needed to ultimately achieve the regulatory approval of a new paediatric dosage form. These clinical trials are usually not captured in the agreed PIPs but can drive up costs substantially.
- Regulatory submission and maintenance fees for paediatric formulations (which often have quite low use and limited shelf life)

- The operating costs of running unfeasible or uninformative trials, which should also be considered within the context of overall finite R&D resources for both paediatric and adult development. Further reflection on pragmatic ways to avoid trials that prove unfeasible or impossible to complete would ensure resources are being dedicated to mutually-agreed relevant paediatric therapeutic needs.

Prioritisation of development programs has to occur within the available R&D budgets, leading to trade-off decisions and possible delays in adult development programs due to allocation of available resources to mandatory PIP programs. This is further complicated by the fact that PIPs are agreed early during development and sometimes years before the actual clinical program is conducted. This creates significant financial commitment for R&D budgets in the long-term and makes resource planning difficult.

Similarly to the operation of other incentives in the pharmaceutical sector, the Regulation therefore aimed at striking a balance between companies' obligations and rewards across the board and not for any individual product.

## 5. Functioning reward system

**Do you agree that the reward system generally functions well and that early, strategic planning will usually ensure that a company received a reward?**

EFPIA agrees the reward system generally functions well but disagrees that early planning alone can ensure that companies receive a reward. The Paediatric Regulation was established on the basis that a system of both obligations and rewards is necessary to achieve its key objectives, namely "to facilitate the development and accessibility of paediatric medicines"[7].

The Regulation therefore recognises that a reward should be granted to companies "for conducting studies in the paediatric population and not for demonstrating that a product is safe and effective"[8]. This means a reward can be granted regardless of whether a paediatric indication is authorised or not, thus recognising the inherent value of generating information – in accordance with an agreed PIP – despite the possible outcome that a product is in fact not suitable for paediatric use. This is consistent with the objective of the Regulation to improve the information available on the use of medicinal products in the paediatric population.

Despite these intentions, it has however often been the case that rewards are not granted or even achievable. In fact, less than half of all completed PIPs so far have led to any type of reward and less than 40% have obtained the SPC 6-month extension reward[9]. Rewards are therefore far from being a certainty when a company engages in the execution of a PIP.

The reward system aims at striking a balance in that rewards will neither be available for every PIP completed nor in every EU Member State. Further, where granted and as the consultation document rightly points out, the reward's value[10] will largely depend on the overall market size and revenue of a

[7] Recitals 4 and 6 of Regulation (EC) No 1901/2006
[8] Recital 28 of Regulation (EC) No 1901/2006
[9] EMA's 10-year Report, *op. cit.,* p. 17 – By the end of 2015, SPC extensions had been granted for 39 medicines, compared to 99 final/full compliance check opinions.
[10] Footnote 6 in the Consultation Document comments that the judgment by the CJEU allowing negative-term SPCs to be granted has increased the 'value' of the reward. EFPIA disagrees with the statement as this judgment has

product at the time of SPC expiry and will therefore greatly vary over the spectrum of pharmaceutical products as well as within the product lifecycle, depending on the number of indications, price renegotiations, etc. This is another strong balancing element, which is inherent to all pharmaceutical incentives and rewards mechanisms. This balance needs to be maintained.

EFPIA agrees that in the first years after the Regulation came into force, many products and PIPs could not achieve a reward because the conditions could not be satisfied in time, before loss of exclusivity. It might therefore be envisaged, as indicated in the consultation document, that as more PIPs are conducted for newer products, this may lead to a greater proportion of products obtaining a reward. However, EFPIA believes that it is not necessarily the case that "better (earlier or more strategic) planning" will generate an increased number of rewards, for the following reasons:

- Given the lengthy timelines for paediatric research, rewards can still be difficult to obtain, even with early planning in the product lifecycle.
- The larger and more complex the development program agreed in a PIP, the lower the chances of completion on time and obtaining the reward.
- PIP feasibility is a major consideration in achieving a reward. For instance, given the rare nature of some diseases, particularly in children, the period of time to recruit sufficient subjects for a trial can be extremely long even when this is allowed for during planning stages. The lack of sufficient numbers of subjects can lengthen study timelines significantly, or even render a trial unfeasible.
- Also, taking a forward looking approach and as the number of indications developed per drug tends to increase, each further indication may require compliance with a PIP for which there will generally be no additional reward possible.

Furthermore, obtaining the reward (other than for orphan products) requires the availability of a SPC. Not all products, even if patent protected, benefit from a SPC. As pharmaceutical research is turning towards development of products for patients with high unmet medical needs, development and regulatory approval timelines may be contracting to support patients' access as quickly as possible. In such circumstances, this faster development may mean that a new molecule will not be able to obtain a SPC at all.

Finally, the availability of SPCs and therefore of SPC extensions has not been equal in all EU countries. According to data from 23 Member States, over the past 10 years, only 322 SPC (national) extensions have been granted for 39 products[11], which means that - on average - a SPC extension has been granted in fewer than 10 countries per product. We expect the entry into force of the unitary patent system and hopefully, ultimately of a unitary SPC, to improve this situation eventually, but not in the short term[12].

merely enabled a very few products to get the reward it was entitled to under the Paediatric Regulation in a very specific circumstance that is not generally applicable.

[11] EMA's 10-year report, *op. cit.*, p. 17

[12] See EFPIA's Proposal for a Unitary SPC here.

## 6. The Orphan Reward

**How do you judge the importance of the orphan reward compared to the SPC reward?**

The orphan reward consisting of a 2-year extension of orphan market exclusivity (Article 37) is as important as the "non-orphan" reward consisting of a 6-month SPC extension (Article 36). They are designed to be mutually exclusive and apply in different scenarios.

The Orphan Regulation was introduced to stimulate the research, development and marketing authorisation (MA) of medicinal products for the treatment of patients suffering from rare conditions, many of which affect children. At an early stage an orphan designation can help to mobilise resources to fund the development, which can be especially relevant for SMEs and academics. An orphan drug designation for example is a criterion for academics to access some of the Horizon 2020 grants for rare diseases. The orphan designation must be applied for prior to an MA application and can be granted to products with or without patent protection. With the granting of this designation, which is based on stringent criteria and a thorough assessment by the EMA's Committee on Orphan Medicinal Products, the company then has access to incentives including protocol advice and upon MA grant a 10-year market exclusivity period, if the criteria are maintained at the time of grant of the MA. In order to obtain an MA, a separate, detailed assessment must be carried out by the EMA's Committee on Human Medicinal Products (CHMP) and the requirements and assessment are the same for all products, whether they have orphan designation or not.

Following authorisation as an orphan medicinal product (OMP), the market exclusivity also has a check point which occurs 5 years after the MA where a re-evaluation can be triggered by a Member State if they believe that the product no longer meets the criteria for an OMP. If this is confirmed to be the case, the 10-year market exclusivity for the product is reduced to 6 years.

OMPs are fully subject to all the obligations under the Paediatric Regulation and upon completion of the PIP are eligible for a 2-year extension of the orphan market exclusivity period. Under the Paediatric Regulation, an OMP protected by a patent or SPC is prevented from obtaining both a 6-month SPC extension and the 2-year extension of orphan market exclusivity[13]. As a result, the sponsor who has fulfilled its paediatric obligations for a product which has a valid patent/SPC must decide whether to maintain the orphan designation and extend the orphan exclusivity for 2 years (with no SPC extension), or to withdraw the orphan designation in order to obtain the SPC extension[14].

EFPIA believes that despite the important role that the orphan reward plays in stimulating research it is also important to continue to allow the sponsor to withdraw the orphan designation when appropriate. This is consistent with the principle that the orphan designation is a choice for the sponsor; it is the sponsor who has to submit an application for orphan designation and who has to submit an application in order to maintain the orphan designation at time of marketing authorisation.

This is also consistent with the application of Article 7(3) of the Orphan Regulation which specifies that an MA granted for an OMP shall cover only orphan indications. Other, non-orphan, indications require a

[13] This is supported by recital (29) to the Paediatric Regulation which refers to the need to prevent a double incentive for orphan medicinal products which are patent-protected.

[14] The availability of this option was endorsed by the Court of Milan (Italy) in a case concerning Novartis' product Glivec (imatinib). Similarly, it was also endorsed by the Provisions Judge of the District Court of The Hague (the Netherlands) in case C/09/500844 KG ZA 15-1829 concerning Novartis' the same product Glivec (imatinib), which also found that in order for an orphan designated product to benefit from the paediatric reward of SPC extension, the removal from the Register has to take place before the application under Article 7 (for a new medicinal product) or 8 (new indication, pharmaceutical form or route of administration) of the Paediatric Regulation is made.

complete and separate MA and therefore cannot be approved as a variation to the orphan MA. The OMP will subsequently be marketed under a different trade name. If a company wishes to maintain a single MA it must withdraw the orphan status for the product. There are several examples where an applicant requested and obtained the removal of a designated OMP from the Orphan Register in order to obtain a single MA for both the orphan and non-orphan indication(s)[15].

Companies should be able to choose the most appropriate reward for their product upon fulfilling the agreed pediatric research and according to the patent/SPC status of the compound. As the two rewards, SPC extension and paediatric exclusivity, are mutually exclusive, this allows companies to receive the incentive for conducting the required paediatric research, without being rewarded twice.

## 7. Improved implementation

**Do you agree that the Regulation's implementation has improved over time and that some early problems have been solved?**

EFPIA agrees that the full complexity of implementing the Regulation was not entirely foreseen, neither by the regulators nor industry. This led to early and continued difficulties with the processes of agreeing and implementing PIPs. EFPIA acknowledges the efforts made by the EC and EMA to make improvements in this regard, including the most recent simplification measures. It is important at all time that the processes and procedures do not impede the scientific dialogue.

However, the complexity in implementing the Regulation is also linked to the complexity of developing medicines for the paediatric population. This impacts PIP content, and improvements are still needed in that respect. Any approach that allows the content of the PIP to be better aligned with the current development status of the compound is strongly encouraged, particularly in paediatric oncology.

EFPIA welcomes opportunities for early dialogue that are scientific in nature, and that can inform how paediatric development should be pursued and integrated into the overall development strategy for a new molecule. A better delineation of roles and responsibilities according to their underlying mandate in the overall regulatory framework should be implemented between the PDCO, CHMP and National Competent Authorities (NCAs) to avoid overlapping activities and ensure the right expertise is available at the right moment.
The 'early paediatric interaction' with PDCO could also be improved. As it is normally followed by CHMP Scientific Advice, any improvement of the interface between CHMP Scientific Advice and PDCO advice would allow companies to have their paediatric research better embedded in their overall research programmes and to progress their PIPs more quickly and efficiently. The PDCO could for example focus on the identification of paediatric needs and determining a high-level development strategy, while CHMP is guiding scientific advice and operational execution of the development program. National regulatory authorities are responsible for ensuring scientifically and ethically robust clinical trial protocols, documentation and oversight.

[15] This means that the European Commission accepts that a removal from the Orphan Register has the legal effect that a product is no longer an orphan designated product and that, therefore, Article 7(3) of the Orphan Regulation does not stand in the way of including all indications (i.e. the former orphan indications and the non-orphan indications) in a single MA.

Global paediatric development programmes need to be better supported, and EFPIA notes with interest the recent communication from EMA on the topic[16], which is a clear step in the right direction. Activities that lead to better collaboration between regions, such as a broadening of the Common Commentary process, are welcome. It is important that companies are allowed to initiate an EMA-FDA common commentary process when needed in order to ensure better awareness and alignment of the two agencies under their respective legal remits. Joint education sessions and publications on paediatric development e.g. lessons learnt, do's and don'ts, would also be helpful.

## 8. Waivers and the "mechanism of action" principle

**Do you have any comments on the above? Can you quantify and qualify missed opportunities in specific therapeutic areas in the last ten years?**

The waiver system is intended to avoid unnecessary research and indeed the majority of waivers up to now (60%) have been granted because the medicine was likely to be unsafe, ineffective or would not provide significant benefit to the paediatric population. As of 2015, 30% of waivers have been granted because the condition occurred only in adults[17]. This percentage is expected to decrease following the revision and revocation of many of the class waivers in 2015[18].

A number of stakeholders have called for a more systematic "mechanism-of-action" (MOA) or target-based approach to paediatric medicine development, especially in cases where waivers are granted because the condition occurs only in adults. It is crucial for all stakeholders that there is predictability in the understanding of the scope of their obligations under the Paediatric Regulation. Hence an approach is required that balances the possibility to address unmet paediatric needs and the need to ensure a clear and predictable scope for paediatric medicines development which is based on robust foundational science, validated targets and feasibility.

Due to the paucity of pre-clinical basic science data related to the mechanisms which drive childhood disease, applying an MOA-based approach will be flawed if it is not data-driven and if it is essentially extrapolation from adult disease into a vulnerable population with little evidence basis. This is especially true for paediatric oncology as most paediatric tumours are due to unique genetic abnormalities whereas adult tumours have significant environmental influences (cigarette smoking, pollution, occupational exposures, sun exposure, etc.) resulting in higher mutational burden (such as seen in lung cancer and melanoma). The IMI-2 pre-clinical oncology program is just beginning and will help inform this discussion about the oncogenic drivers of paediatric tumours – this is the kind of data that is needed to support transition to MOA approaches. Furthermore, the difficulty may be compounded where there are many tumor types and each type may have its own profile and susceptibility to the MOA. The MOA may not be the same in the adult and paediatric population and there may be a different expression of the target in the younger population.

In addition, because of the relatively small paediatric cancer populations overall, having to do studies in still smaller sub-populations or rare populations (eg. subsets of paediatric patients with certain mutations) tends to result in lengthy recruitment times and the strong possibility that the trials may be

[16] EU-USA strategic meeting on the future of paediatric medicines http://www.ema.europa.eu/docs/en_GB/document_library/Report/2016/12/WC500218004.pdf
[17] EMA's 10-year report, *op. cit.,* p. 26
[18] The PDCO adopted a review of the class waiver list on 23 July 2015 (CW/0001/2015).

unfeasible and could never complete, especially if there are several sponsors with agents directed against the same target mutation competing for the same small subset of patients.

EFPIA has therefore proposed to that purpose an approach, which relies on:

1. A comprehensive inventory of disease-based unmet paediatric needs, based on the existing requirements of Article 43 of the Paediatric Regulation, to indicate clearly for each need if there is research on-going and if so, what type of research, ensuring visibility to all stakeholders of areas where research is most needed and avoiding that the paediatric population is subjected to un-necessary or unfeasible clinical trials. It should include, specifically for paediatric oncology needs, references to scientific publications on tumour target identification and validation that support a particular oncology need. Multiple stakeholders (industry, regulators, epidemiologists, patient groups, paediatric networks) should be involved in this assessment for review by PDCO.

2. Revising EMA policy on the determination of the conditions for a PIP/waiver to ensure a clear and predictable understanding of the references framing the discussion for potential paediatric development plans, particularly in the field of oncology. This Policy already allows a MOA approach, and the proposal is to further refine it in conjunction with the inventory described above. In their discussion on whether to request a full PIP or to grant a waiver, PDCO (and companies) would use the inventory to identify the area of unmet need to focus on, based on the adult condition; for oncology products, if the adult condition is not a suitable basis for the PIP, the MOA should be used to identify the most plausible, validated paediatric cancer target with an unmet need. In all cases, the discussion would also take into account the feasibility of the trial(s).

Such a structured, scientific, prospective and agreed identification of paediatric needs could provide predictability which would be beneficial and is likely to result in an increase of scientifically justified paediatric development focused on those areas where significant benefit is to be expected. This would further help avoid trials that prove unfeasible or impossible to complete and would ensure resources are being dedicated to mutually-agreed relevant paediatric therapeutic needs.

Already now, companies have evolved in their approach to the development of drugs for specific paediatric indications, spurred by the Regulation but also their better understanding of the diseases that affect children. This is reflected for example in the oncology area, as reported in the EMA 10-year report[19], with companies having proposed voluntary PIPs for 11 out of the 27 (more than 40%) of the conditions covered by class- or product waivers.

## 9. Deferrals

**Do you agree with the above assessment of deferrals?**

Deferrals are only agreed by PDCO when either the information on benefit/risk in the adult population is not sufficient to justify the start of clinical trials in the paediatric population, or for technical feasibility reasons. Scientific reasons may include the need to clarify the adult dose and obtaining information on drug interactions. Hence deferrals are often critically important to protect the paediatric population and prevent unnecessary and unethical trials. In addition, deferrals for feasibility reasons are important and the aim of the Paediatric Regulation is clearly not to have a negative impact on adult drug development.

[19] EMA's 10-year Report, *op. cit.,* p.58

Hence EFPIA believes deferrals have only been granted by PDCO for sound, justified and scientific reasons and are necessary to avoid unsafe and unethical trials at a specific point of time.

Long deferrals should not be seen as an advantage for companies, as not completing their agreed PIP in time within the applicable deadlines can compromise the availability of a reward.

The fact that a product is already on the market may make it more difficult to recruit patients into clinical trials, whether children or adults – the reasons for this are not well understood and should be further explored. Other educational, logistical, ethical or societal barriers may contribute significantly to patient recruitment issues.

With respect to the observation that long deferrals would undermine the enforceability of the paediatric requirements, it needs to be noted that whenever deferrals have been agreed with PDCO for authorised products, the MAH needs to submit an annual report to demonstrate its progress in accordance with the agreed PIP, including the timelines. Furthermore, as referred to in Article 49.3, there is a penalties regime in place to enforce relevant obligations under the Regulation, under which the Commission may impose significant financial penalties for infringement[20].

## 10. Voluntary PIPs

**Do you have any comments on the above?**

EFPIA appreciates the Commission's confirmation in the consultation document that a paediatric investigation plan may be agreed voluntarily even if the applicant is entitled to a waiver under Article 11(1)(b), and that such a voluntary paediatric investigation plan would be eligible for a reward under the Regulation, thereby serving as incentive.

EMA's 10-year Report[21] describes 14 voluntary paediatric investigation plans in the area of oncology up to December 2015. It should be noted that a voluntary paediatric investigation plan, once agreed, entails the same binding obligations and challenges as mandatory ones, so cannot be undertaken lightly. To encourage more voluntary paediatric investigation plans where waivers are entitled, EMA and Commission may need to do more to promote this possibility and explain the practicalities to companies, potentially in conjunction with an improved inventory of therapeutic needs.

## 11. Biosimilars

**Do you have any comments on the above?**

The development of biosimilar medicines and the mechanism by which they are reviewed and approved require the conduct of clinical studies to demonstrate comparability to the applicable reference innovator product. Demonstration of biosimilarity in one or more indications may allow for extrapolation to other indication(s) of the reference product with appropriate scientific justification. As indicated in the Consultation document, it would therefore not be justified to repeat paediatric trials for these products, either from a scientific or an ethical perspective.

[20] Regulation (EC) No 658/2007, as amended (Penalties Regulation)
[21] EMA's 10-year Report, *op. cit.,* p. 58

The approved indications of biosimilar medicines will generally reflect those of the innovator product, including paediatric indications, where applicable and provided such indications are accessible from an IP perspective. The administration to paediatric patients very often requires the development of additional presentations that are suitable for accurate dosing for children. For example, a pre-filled syringe is used for adults vs. a vial for children or a lower strength or concentration of the product is needed for different age or weight classes. Since the development of these paediatric formulations requires more investment and more time, the biosimilar developer may or may not decide to develop the product suitable for paediatrics.

In the rarely occurring situations where the biosimilar does not have a specific presentation or dosing device suitable for administering the correct dose for paediatric administration, this would be a matter for regulatory review and regulators may decide not to approve the biosimilar product for paediatric use. Also, in this situation the risk management plan would need to address and mitigate for any risks arising as a result.

Furthermore, as mentioned in the consultation document, there are mechanisms in place under the Regulation to ensure that the originator product – including the paediatric use indication – remains on the market.

## 12. PUMA

**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?**

EFPIA agrees that the PUMA has proved to be a disappointment, as demonstrated by the fact that so few have been sought or granted. The reasons for this are quite well known.

A PUMA is granted to off-patent products which are usually already subject to generic competition. The 10-year period of data and market protection it provides is necessarily specific to the paediatric data/indication on which the PUMA is based, and therefore restrains generic applications for that particular indication and their reliance on that particular data only. In other words, generics may not then be authorised for the paediatric indication in question, during the exclusivity period. However, despite the innovative company having invested in the preparation and conduct of the PIP and associated regulatory procedures, the resulting PUMA is unlikely to be of any sufficient commercial value, given the generally small populations and market returns on paediatric indications. Furthermore, unless there is a very specific new paediatric formulation associated with the PUMA, generic products will in many cases be prescribed 'off-label' (or more precisely, 'cross-label') for the newly authorised paediatric indication – thereby providing much of the (already limited) benefit of the innovative company's investment directly to its generic competitors.

The key to the exclusivity 'gap' is addressing this issue of cross-label use which has a similar impact on all the other indication-specific rights and protections, which should theoretically incentivise R&D into existing medicines for new uses. As well as PUMAs this includes the data exclusivity provided for well-established substances, second medical use patents and in some cases orphan market exclusivity. However, as indicated in the consultation document, solutions in this context are generally outside the scope of the Paediatric Regulation and even EU competence, since they concern prescribing, substitution, pricing and reimbursement practices in the Member States. Similarly, the problem of

insufficiently supportive price and reimbursement models (not recognising the added value of a PUMA product compared to unlicensed/cross-label use of generic products), which are needed to facilitate and sustain market access of products with new paediatric indications, is not within the scope of the Regulation or within EU competence.

It is interesting that the provision of external funding from the Commission for off-patent medicines research projects has rarely led to an authorised product; from this it can be concluded that even that may be insufficient to overcome the factors referred to above.

Notwithstanding the disappointing results to date of the PUMA, and the reasons for this described above, EFPIA would **not** advocate abolishing it, because if the PUMA encourages even a few new paediatric developments, it is worthwhile having it.

As a pragmatic measure, EFPIA is of the view that paediatric development via the PUMA might be encouraged somewhat if it could be clarified, as a matter of interpretation and process (e.g. in the PIP application form) that if the conduct of an agreed PIP endures beyond the patent/SPC protection period, it should automatically be converted into a PUMA. This measure would align with the statement in the EMA's 10-year Report[22] that "any agreed PIP could potentially be used to apply for a PUMA when the medicine's patent has expired". At present, because the legal basis of the PIP has to be indicated in the application form, applicants may be under the impression that a PUMA may not be a possibility for a PIP that has been applied for under Article 7 or 8. Confirming this point could provide more legal certainty that some incentive will be available, even for long-running PIPs, and improve the number of completed PIPs in the future.

Also, greater awareness raising and 'promotion' of the PUMA by the EMA/EC may be helpful, although public funding is also likely to be needed to generate materially more interest, potentially among academics and SMEs as well as larger companies.

## 13. Scientifically valid and ethically sound clinical trials with children

**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?**

The conduct of paediatric clinical studies has specific challenges which can range from the completion of the informed consent form (e.g. signature by either one or both parents on behalf of the child depending where the study is run) to laboratory issues (e.g. how much blood can be taken and at what frequency).

As stated in the consultation document, the questions around ethics and scientific validity of a clinical study in children are already considered by the EMA's paediatric committee (PDCO) and at a national level by relevant Ethics Committees and Competent Authorities. Whilst these rigorous review steps are important, there have been cases where Ethics Committee approvals for a paediatric clinical study have been difficult to obtain (either due to a lack of experience by the Ethics Committee or expression of a different view). Any steps to increase the alignment between clinical study decisions by the PDCO and at Member State level (and with other non-EU regulatory authorities) would help with clinical study initiation.

[22] EMA's 10-year Report, *op. cit.,* p. 15

Recruitment of paediatric patients into clinical trials can also be difficult. Many diseases occur infrequently in children and low patient numbers often do not allow fully powered efficacy studies to be conducted or lead to unacceptably extended timelines for completing those studies. The EMA's 10-year Report[23] highlights that patient recruitment issues are the most frequently reported difficulty with paediatric clinical studies in the Paediatric Investigation Plan (PIP) (in 36% of cases). In addition, as companies develop compounds for the same indication, they are competing for the same patient pools. The inventory of paediatric needs suggested by EFPIA (see response to question 8) can ensure that such 'crowding' does not occur, and that trials are carried out where most needed.

Due to trial duration, studies are often now enrolling paediatric patients that become adults during the study or reach puberty, so the study needs to be designed to cover these different age ranges or otherwise adapted. The complexity of designing studies that can handle such changes must not be underestimated.

It may not be possible to enrol paediatric patients into a single clinical study when the disease incidence is very low and patients are too geographically dispersed, as the logistic of running the study become too disruptive for the patients, who e.g. may need to travel to study centres that are far away from their homes. Several other factors, such as differences and changes in epidemiology, national treatment guidelines or immunisation programmes and availability of comparator products, may also impact the feasibility of a trial. This issue can be exacerbated in situations when there are several medicines being studied for the same indication or condition during a similar timeframe. Differences in approach to paediatric development between different jurisdictions, particularly the EU and US can also make a single clinical study unfeasible. Recent announcements regarding closer alignment on paediatric development between the EMA and FDA, via the paediatric cluster, are therefore welcomed. The emphasis on a common scientific approach to paediatric medicine development, as proposed in the latest draft of addendum R1 to ICH E11[24] is a positive step and should be further implemented.

Data presented in the EMA's 10-year Report illustrate that there was a consistent and stable number of authorized paediatric clinical trials planned for each given year between 2006-2015 (ranging from 329 (in 2014) to 424 (in 2009) trials initiated in a single year), whilst the proportion of new paediatric clinical trials compared to all newly initiated clinical trials has increased slightly from approximately 9% in 2006 to approximately 11% in 2015[25]. However, whilst the initiation of clinical studies is one measure of the impact of the Regulation, the timely completion of clinical studies is perhaps a more important measure. Some of the patient recruitment issues highlighted in the previous paragraphs have led to paediatric clinical studies which whilst on-going, are unlikely to be able to complete within a reasonable timeframe. In these cases, there is a need for a EU cross-stakeholder agreement on the criteria to identify those paediatric clinical trials that will not be able to complete in a reasonable time and need for EMA/PDCO guidance on how these should be handled. Indeed, inclusion of patients in trials that will not be able to finalise is unethical.

The feasibility of clinical studies is therefore an important consideration which needs to be considered early in paediatric drug development. Specific criteria to guide consistent decision-making need to be developed in a multi-stakeholder workgroup to ensure they consider epidemiological and operational criteria. In addition to the standard clinical development approach to paediatric medicine development, newer approaches that may provide similar conclusions with a better utilisation of existing data e.g. physiologically-based pharmacokinetic (PBPK) modelling, extrapolation of adult data to paediatric

[23] *Ibid.*, p. 43
[24] Guideline on clinical investigation of medicinal products in the pediatric population EMA/CPMP/ICH/2711/1999 (R1)
[25] EMA's 10-year Report, *op. cit.,* p. 40

populations should also be encouraged and used whenever possible[26]. EFPIA welcomes these recent developments that may help to simplify clinical trial design and reduce the requirement for clinical studies in paediatric patients. In addition, the opportunity for early dialogue between regulators, industry and patients may also help to identify feasibility issues at an earlier stage, and lead to proactive proposals to address them e.g. modelling, extrapolation or inclusion of paediatric patients into adult studies in certain cases.

Other innovative approaches to clinical trial design, such as mechanism of action-based approaches, multi-agent multi-sponsor master trials, or the use of existing registries or real-world data-based evidence generation for paediatric indications have been used, and should be utilised and encouraged wherever possible, to both reduce the time for development and unnecessary clinical testing in children.

It would also be beneficial to include both paediatric networks and patient organisations in clinical trial design. Paediatric networks / academic experts could be leveraged at an early stage to advise PDCO on study design and feasibility, including whether parents are likely to enroll their children into them. Patient organisations could help increase recruitment and retention rates and provide support to children and parents participating in studies.

Finally, in some cases there are gaps in the understanding of the pathology of childhood diseases which also impacts on the ability to run clinical trials in paediatric patients. These gaps in basic research must be closed via academic or pre-competitive research to focus clinical research in paediatric indications corresponding to the most pressing needs. This issue has already been recognised in the adult medicine field and triggered many new IMI projects.

## 14. Financial sustainability

**Do you have any views on the above and the fact that the paediatric investigation plan process is currently exempt from the fee system?**

EFPIA acknowledges the significant investment of resources required to be applied on the part of the Member State authorities in supporting the activities of the EMA under the Paediatric Regulation, and notes also the significant resources required to be invested by its member companies in terms of R&D and administrative efforts in complying with the Regulation.

In EFPIA's view it has been appropriate not to charge any fees as the Regulation has been introduced and become established. If this were to change, the imposition of fees for PIP/waiver applications and modifications could discourage companies from engaging earlier with PDCO, given the uncertainty of the outcome of their R&D programmes, the complexity of the administrative process and potential for multiple subsequent modifications[27].

EFPIA notes that Article 48 of the Paediatric Regulation states that the "Community contribution provided for in Article 67 of Regulation (EC) No 726/2004 shall cover the work of the Paediatric Committee, including scientific support provided by experts, and of the Agency, including the assessment of paediatric investigation plans." We suggest, therefore, that the financial provisions of the EMA should first be reviewed, to ensure that the Community (Union) contribution to cover these activities is appropriately distributed to reimburse national experts.

[26] For instance, the FDA can approve extrapolation to paediatric labeling using PK data alone.
[27] For example, there have been between 2 and 7 modifications to the PIPs for the 9 oncology products for which a compliance check was issued.

## 15. Positive impact on paediatric research in Europe

**How do you judge the effects of the Paediatric Regulation on paediatric research?**

EFPIA believes that the Paediatric Regulation has had a positive impact on paediatric research in Europe and recognises the value of the existing research frameworks. However, compared to research for adult diseases, paediatric research is still evolving and shall be further strengthened in the coming years.

EMA has established a European Network of Paediatric Research which incorporates almost 40 networks eight years after launch. Paediatric Networks that provide a reliable and timely research output are valuable partners for industry but EFPIA believes that EnprEMA could be better leveraged to become a valuable contributor to the actual conduct of paediatric clinical trials. Closer collaboration with patient organisations could improve recruitment and lower drop-out rate in paediatric studies.

While the Regulation has increased the number of paediatric clinical trials with a growing number of children involved in clinical trials, it has not provided the infrastructure needed to perform these trials effectively.

EMA's 10-year Report mentions that the lack of infrastructure has been identified by EnprEMA as the major hurdle to sustainable paediatric research[28]. EFPIA is aligned with EMA's conclusion that a common infrastructure to support the existing networks and allow them to collaborate effectively and offer high quality services to industry when developing medicines for children would be a valuable addition for the EU. It would be helpful to establish a better stratification of the different networks and their contribution at EnPrEMA and establish a bigger multi-stakeholder coordinated approach such as the proposed IMI project for a pan-EU paediatric clinical trial network (call issued in December 2016[29]).

In addition, EFPIA sees a need for more public funding to be allocated to foundational and translational research by academic institutions to enable a better understanding of the biology of some paediatric diseases, especially in the areas that are not yet well understood (e.g. paediatric tumours). A better inventory of paediatric unmet research needs in close collaboration with multiple stakeholders (industry, regulators, epidemiologists, patient groups, paediatric networks), as suggested by EFPIA, may help identify areas where data is lacking and further research is needed.

EFPIA also believes that more public funding should be allocated to academic and pre-competitive research to develop new methodologies or close data gaps to address current bottlenecks and enable development in paediatric needs areas in close collaboration with relevant stakeholders. An example is the work done at the level of the Innovative Medicines Initiative with the 7th IMI2 call aiming at establishing a comprehensive 'paediatric preclinical proof-of-concept platform' to enable clinical molecule development for children with cancer.

[28] EMA's 10-year Report, *op. cit.*, p. 82
[29] Please see IMI call here.

## 16. Emerging trends and the future of paediatric medicines

**Are there any emerging trends that may have an impact on the development of paediatric medicines and the relevance of the Paediatric Regulation?**

While EFPIA agrees with the trends identified by the European Commission, it believes the Regulation can continue to work in the context of new emerging research paradigms if a pragmatic approach is adopted.

In particular, EFPIA sees a need for the EMA to take the regulatory acceleration procedures into consideration e.g. adaptive pathways and PRIME scheme applied to an adult development programme, which can make the requirements of the Paediatric Regulation even more challenging for companies to comply with from a timing perspective. These accelerated pathways may impact the scope, timing, content and conduct of PIPs, just as precision medicine may impact the scope of the paediatric population in PIPs and the definition of waivers.

EFPIA suggests further scientific and technological trends should be considered, especially new and innovative approaches to clinical trial design that can help minimise the need for testing in paediatric patients and therefore have an impact on the implementation and even relevance of the Paediatric Regulation. In particular, the application of physiologically-based pharmacokinetic modelling (PBPK) and the introduction of recent initiatives such as the EU extrapolation framework are encouraging and fully supported by the pharmaceutical industry as mentioned in our response to consultation item no. 13.

Other innovative approaches to clinical trial design, such as the use of existing registries or real-world evidence generation for paediatric indications, could also reduce the time for development and unnecessary clinical testing in children. Similarly, innovative ways to interact with paediatric populations, e.g. through patient organisations and/or high technology devices such as smartphones which may change their understanding, approach and participation in clinical trials, could have an impact on the way PIPs are designed and conducted.

## 17. Other issues

**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?**

The pharmaceutical industry is committed to the important task of developing medicines suited to children and believes considerable achievements have been reached in this field since the entry into force of the Paediatric Regulation, which has contributed to make paediatric research an integral part of general medicines development. This is reflected in the 937 PIPs approved by EMA between 2007 and October 2016, of which 113 have been successfully completed[30]. However, paediatric development remains challenging and companies are trying to overcome the hurdles of conducting research in children, including study feasibility, ethics committee approvals, and global paediatric development, through dialogue with regulators and paediatric networks.

To that purpose, EFPIA would like to flag a number of other issues of relevance to the implementation and success of the Regulation and which would require further consideration by the Commission, regulatory authorities or Member States.

[30] As per EMA website on 5 October 2016.

- EFPIA believes that an unnecessary degree of **bureaucracy** has been introduced in the current procedures, which unnecessarily hinders the implementation of the Paediatric Regulation, while clearer and simpler procedures, together with a certain degree of flexibility, could help achieve better results and more efficiently, for companies, authorities and critically for patients. Specific examples relate to the administrative burden and delays resulting from the current PIP Modification process or from the PIP compliance check. These practical issues result from the fact that too much detail of the whole development program is requested in the PIP at a very early stage. To address these issues, EFPIA would advocate for an optimised process for dialogue on paediatric development plans, allowing the creation, agreement on and conduct of the PIP to fit more naturally within the drug development process. In addition, a simple procedure for urgent access to the PDCO and a more proportionate compliance check process, taking into consideration potential impact on public health of any delay in products' availability, would be beneficial. In particular, partial compliance checks should be reconsidered as these are not required by the Regulation and can further delay submission.

- **Paediatric clinical trials** which are agreed with the PDCO - on which all Member States are represented - should in principle be authorised by the national competent authorities and ethics committees via the Clinical Trial Application process. This is not always the case and this lack of alignment needs to be addressed.

- The Paediatric Regulation has led to many new paediatric indications and formulations being developed by companies for existing products, as required under Article 8 of the Regulation. However, the added value of these is a subject of debate at national level and there are instances of worsening of **pricing and reimbursement conditions** for the product in some Member States or of non-reimbursement in others. This should be addressed in order to ensure availability of these new indications and formulations to children.

- Finally, as most paediatric product development is carried out globally, an **aligned approach of global regulators** on the important elements of a paediatric development program would be a major step towards enhancing efficiency of paediatric drug development, reducing unnecessary clinical trials in children by agreeing studies that are suitable to meet both regulatory requirements worldwide and helping to ensure that children have faster access to new medicines. For example, we welcome the recent announcement by EMA on close collaboration with FDA. In addition to what is foreseen, we would also like to suggest the following be included:
    1. The establishment of a joint procedure as an additional option to allow for a common and aligned timeline for content and submission of paediatric development plans to FDA and EMA, which can occur at any time before commencement of the adult pivotal clinical investigations. Such a joint procedure should be voluntary. The industry believes that establishing a joint voluntary procedure is achievable under the current legal framework, in that the EU paediatric regulation provides enough flexibility to allow for a joint procedure with the US while achieving the current submission timeline requirements. Such parallel submission of plans would make a significant contribution to facilitating efficient paediatric drug development while reducing procedural rework (i.e., amendment/revision) and aiming at conducting global paediatric programmes and studies and addressing unmet need for paediatric populations in both regions.
    2. FDA and EMA should continue existing efforts aimed at streamlining the procedures for submitting paediatric development plans.

3. FDA and EMA should consult with each other, and with industry, when either agency undertakes to prepare new guidelines governing the submission of paediatric development plans.
4. FDA and EMA should expand established procedures for regular consultations with each other regarding paediatric development plans evaluated separately by both agencies. A sponsor submitting a paediatric development plan to both agencies should also be given the opportunity to request a joint discussion of the plan with FDA and EMA.