

# Consultation in relation to the Paediatric Report

*Ref. PCPM/16 – Paediatric Report*

## 1. PART I - GENERAL INFORMATION ABOUT RESPONDENTS

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**If you are a business, please indicate the size of your business**

- Self-employed
- Micro-enterprise (under 10 employees)
- Small enterprise (under 50 employees)
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- Large company (250 employees or more)

**Please indicate the level at which your organisation is active:**

- Local
- National
- Across several countries
- EU
- Global

## 2. PART II – CONSULTATION ITEMS

*(You may choose not to reply to every consultation items)*

### 2.1. More medicines for children

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

I agree that there was a need for the incentive to encourage development in the paediatric population, however, the way the regulation is implemented needs review. There has been insufficient consideration of how to streamline by possibly encouraging industry collaboration and looking for potential for extrapolation e.g. from adults. It is the case that over time the bar does appear to have become higher, which is demonstrated by class waivers that have been revoked as well as further expansion in development plans.

Further, the Regulation has been applied as a blanket approach without considering the many ways new products are developed or repurposed. It seems fair to assume that the paediatric regulation was designed for NCE and new biologicals being developed from scratch in a single linear timeline in the EU, however many products do not fall into that category. A number of products may have been developed by small non-global companies in, for example, the US and only brought to the EU market late in development, and so will come late to the paediatric process and require deferrals to avoid delaying development in adults. Further, many reformulations or repurposing of older products that would still use an 8(3) route mean that the development programme is not conventional and therefore the regulation presents a unique challenge to work out when to submit a PIP and a deferral is then also required. Often with this latter category the DCP process is used which means that the reward is also not forthcoming. If the DCP route is used and 1 or 2 countries are not included (or they decline to approve the product) there is no financial return for the cost of the PIP. Additionally there are countries with limited turnover which results in the risk that the MA ceases to be valid before the PIP is concluded.

### 2.2. Mirroring paediatric needs

**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?

On the contrary, I would consider that the potential requirement for development of different strengths or delivery systems might dissuade companies with more limited resources from developing new treatments. It is interesting to note that PIPs appear earlier in developments where the indication offers full waiver whereas for indications applicable to children companies would appear to consider the PIP close to filing for an adult indication. The Regulation has also impacted the legal basis that is being chosen by companies, for example more companies are trying to use the 10(3) route to avoid perceived delays and costs associated with PIPs although this can mean that there are unnecessary studies against EU reference products in order to comply with the legal basis.

### 2.3. Availability of paediatric medicines in the EU

**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?

There is no substantial market increase for paediatric medicines. There is still pricing driving the use of non paediatric medicine to be used instead of the newer licensed more expensive ones.

### 2.4. Reasonable costs

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

I consider that the costs will largely depend on the therapy area. Overall there is a tendency to underestimate time and costs to fulfil the PIP.  
Furthermore, cost is also dependent on the indication which in some instances demand very large

and therefore very expensive studies.

## 2.5. Functioning reward system

**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?

No, I do not agree. We consider that given the conditions applied to the rewards it is highly unlikely that many companies will recover the development costs, especially for companies and products that do not use the centralised procedure for authorisation and do not wish to commercialise in all member states.

## 2.6. The orphan reward

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

The rewards for orphan products generally are better understood, are automatic and are considered more worthwhile, however, as with SPC this is focused on centralised licensing, meaning that companies which do not choose this procedure will not benefit from either of the rewards.

Overall, a system more similar to orphan rewards for completion of a PIP would be preferable.

## 2.7. Improved implementation

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

No. Although there was some confusion about logistics of the process in the early days e.g. availability of pre-submission meetings, the general feeling is that the process is now much stricter, requests for modification at day 60 are the standard and more burden is being put on pharmaceutical companies due to scope creep.

The clinical burdens appear to be increasing and presumably duplicated company by company. A fundamental issue that has not been removed is that the PDCO and Competent Authority can and do have divergent opinions on paediatric clinical data requirements and study design. Even though it is recognised that those Competent Authorities have representatives on the PDCO, the range of therapeutic areas covered by the PDCO means that they may never represent the opinions of the therapeutic teams within agencies.

It is essential that the requirements placed on companies by the PDCO are agreed by the representatives with their CA. It is not uncommon for individual countries to disagree with the PIP leading to further studies being required. There have been instances where, during review of the dossier in the past, the CA disagreed with the design of the study run, which was previously agreed in detail with PDCO. While better, more forward looking development programmes could improve the financial and time based aspects of the Regulation, these two issues must be addressed (in particular for non-centralised applications).

## 2.8. Waivers and the 'mechanism of action' principle

**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?

I believe that the concept of 'mechanism of action' overlooks the financial burden of clinical studies in less populous diseases and waivers are too rarely applied and do not reflect the logistical difficulty of finding an adequate number of patients and conducting the studies requested. If there were more commercial incentives or broader acceptance of 'mechanism of action' versus requiring empirical evidence, then this argument might have greater merit.

The trend towards looking across 'mechanism of action' is very concerning and can be detrimental to development of new products as a whole. PIPs should ideally focus on the indication that the company is developing in, there should be additional reward for developing under the 'mechanism of action principle', but it should not be legally binding and therefore discouraging development in general.

Additionally, more thought should be given to PIPs for products that are not ‘new’. This is in reference to reformulations of old molecules or new versions of well-established combinations. For constituents that are already widely used in other similar combinations to the new product it could be viewed as unnecessary and even unethical to conduct clinical studies. Further consideration could be given to minimising the requirements in such cases where effective treatments are already available for children.

## 2.9. Deferrals

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

We strongly believe that deferrals are essential both ethically and financially. They are essential to companies to firstly establish that their product is safe and effective prior to treating children, and they also ensure that development in the adult indication is not delayed. We agree that deferrals may not be necessary with some products if the PIP is agreed in a timely manner, but as submissions for PIPs occur later for certain types of products and scenarios, e.g. for those developed in the US and only brought to the EU market late in development, they become increasingly necessary.

## 2.10. Voluntary paediatric investigation plans

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

Our view is that most companies would want to extend their products for use in children, especially if a more pragmatic and inventive approach were considered rather than simply duplicating extensive clinical programmes in various age populations from 0-18. Further, the incentives available are considered to be limited and difficult to obtain, especially with some of the older products that could benefit from a voluntary PIP, but are unlikely to do so because they will be approved outside of the centralised licence system and will not receive a reward.

## 2.11. Biosimilars

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

No comment.

## 2.12. PUMA — Paediatric-use marketing authorisation

**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?

Yes, we are in agreement that the PUMA concept has been a disappointment and suggests that the Regulation has been an excessive measure taken with the aim of solving a minor issue whereas the reality is that physicians and pharmacists have often been capable of delivering therapeutic options from the available adult presentations. More incentive for paediatric presentations and more scope for more positive (age-directed) naming and labelling might be a solution to this problem.

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

**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?

We are in agreement with the analysis of the issues that paediatric programmes create, especially at the operational / recruitment level. The conclusion regarding lack of collaborative programmes is also correct but unless there are significant incentives of being first in a paediatric population rather than competitor companies being required to duplicate extensive clinical paediatric programmes then this will continue to be the case. An additional issue in recruitment of patients for studies with, for example, products which are reformulations of well-established combinations is that it is not just the parents who do not see the value in their children participating in trials, it is also very difficult to find investigators who are at all interested in taking part as many of them simply are not interested in demonstrating that another additional version of a proven mechanism works.

## 2.14. The question of financial sustainability

**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?

Our view is that the PIP requirement is already seen to be an unavoidable additional regulatory burden and a significant financial investment for very little incentive or return. In reality a fee would be relatively trivial within the overall clinical and development costs however would appear to be contrary to how the system is meant to incentivise industry.

## 2.15. Positive impact on paediatric research in Europe

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

No comment

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

**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?

The need for paediatric studies is accepted by industry, however the PDCO/ PIP process is prescriptive and rigid. Introducing development of paediatric medicines into the concept of an adaptive pathway would appear a potentially flexible and potentially more strategic development plan. Further the PDCO could consider adopting a holistic view of those redeveloping and reformulating older products and looking across what is on the market, how burden could be shared and what the most efficient way to gain data in the paediatric setting is.



## 2.17. Other issues to be considered

**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?

No, whilst it can be agreed that that the paediatric regulation was and is needed, its implementation to date does not reflect what was hoped. It was expected to be a mechanism that incentivised research to support paediatric patients but has become onerous on pharmaceutical companies wishing to develop new and known substances with incentives that cannot be claimed by many affected. Further, the scope creep, especially under the 'mechanism of action' principle, can be viewed as a limitation to development and it was not expected that this would occur and may act to deter development of some products by negatively impacting the commercial viability of the product.