

Consultation in relation to the Paediatric Report

Ref. PCPM/16 – Paediatric Report

1. PART I - GENERAL INFORMATION ABOUT RESPONDENTS

Your name or name of the organisation/company: Children's Medicines Working Party / European Forum for Good Clinical Practice (EFGCP)

Transparency Register ID number (for organisations): in process

Country: Belgium

E-mail address: secretariat@efgcp.eu

Received contributions may be published on the Commission's website, with the identity of the contributor. Please state your preference:

- My contribution may be published under the name indicated; I declare that none of it is subject to copyright restrictions that prevent publication**
- My contribution may be published but should be kept anonymous; I declare that none of it is subject to copyright restrictions that prevent publication
- I do not agree that my contribution will be published at all

Please indicate whether you are replying as:

- A citizen
- A business
- A non-governmental organisation (NGO)
- An industry association
- A patient group
- A healthcare professional organisation
- Academia or a research or educational institute
- A public authority
- Other (please specify): Multi-stakeholder association**

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

- Self-employed
- Micro-enterprise (under 10 employees)
- Small enterprise (under 50 employees)
- Medium-sized enterprise (under 250 employees)
- 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?

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?

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 Have existing treatments been replaced by new licensed treatments?

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?

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?

2.6. The orphan reward

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

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?

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?

2.9. Deferrals

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

2.10. Voluntary paediatric investigation plans

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

2.11. Biosimilars

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

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?

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?

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?

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?

The Children's Medicines Working Party (CMWP) is a multi-stakeholder working group of the European Forum for Good Clinical Practice (EFGCP). Our membership includes patient advocates, investigators, regulated industry, academics, contract research organisations, and health authorities. The CMWP promotes the highest scientific, ethical, safety, and quality standards for the design, conduct, and analysis of biomedical research and medicines development for children of all ages. The main objectives of the CMWP are: (1) identifying issues and best practices in order to develop harmonized solutions related to the practices of paediatric research and clinical trial designs in a global context; (2) establishing and maintaining effective cooperation with European and International organizations, including policy makers, patient organizations, regulators, academic societies and professional organisations; and (3) developing and publishing recommendations in order to contribute ethically and scientifically sound development processes, research practices and increase access of children to effective and safe medicines.

The CMWP believes that our representative make-up of multiple collaborative stakeholder groups, allows us a unique opportunity to reflect on the 10 years of implementation and the lessons learned from the application of the Paediatric Regulation. Our varied membership has aligned to provide the following general statements for consideration by the Commission as it analyzes and develops its final report. These statements reflect our direct experience and observations, as well as provide insights incorporated from discussions in numerous forum at varied stakeholder meetings and public conferences. We believe that these positions, when considered, will help to positively evolve the framework within which the Regulation is implemented, facilitating a more favourable environment within which to develop medicines for children in Europe.

The CMWP agrees that the Paediatric Regulation has had an important impact on the development of paediatric medicines in the EU. Over the past 10 years, there has been a steady increase in the number of new paediatric indications for products approved through the centralized procedure (Table 1 – EMA 10-year Report to the EC). In addition, there has been a great momentum toward enhancing the collection of natural history data, generation of basic science research, incorporation of young person's considerations into clinical research and trial design, organization and strengthening of clinical research networks and contract research organizations, and incorporation and strengthening of paediatric-specific expertise in industry and within regulatory agencies. There is a much more concerted effort around early strategic considerations in paediatric medicinal product development, and, there is a movement toward multi-stakeholder collaboration to ensure the value and efficient development of medicinal products that will provide meaningful benefit to the paediatric population.

It is the position of the CMWP that the authors clearly had the needs of the child at the center of their intentions when drafting the Recitals and Articles. The aims, found in Recital 4 of Regulation (EC) No 1901/2006, clearly state the objectives of the Regulation:

“This Regulation aims to facilitate the development and accessibility of medicinal products for use in the paediatric population, to ensure that medicinal products used to treat the paediatric population are subject to ethical research of high quality and are appropriately authorized for use in the paediatric population, and to improve the information available on the use of medicinal products in the various paediatric populations. These objectives should be achieved without subjecting the paediatric population to unnecessary clinical trials and without delaying the authorisation of medicinal products for other age populations.”

It is our perspective that the Regulation continues to address the needs of those children affected by the many varied diseases that innovative medicinal product development is intended to address today. At times, however, these aims have not been able to be fully realised due to lack of sufficient infrastructure to support paediatric medicinal product development, one size fits all approaches to address paediatric needs, and/or overly burdensome and rigid implementation. It is our position, that

as written, the Regulation can fulfill its intended aims with a more pragmatic implementation that makes room for flexibility on a case-by-case basis.

To address this proposal we have provided our response utilizing the stated aims of the Regulation as our construct.

- “... to facilitate the development and accessibility of medicinal products for use in the paediatric population, ...”

The CMWP believes that there is ample evidence to substantiate that Regulation (EC) No 1901/2006 has facilitated a more focused movement toward early strategic thinking on the development of innovative medicinal products. While this is an important success of the Regulation, as implemented, there has been no consideration of how to prioritize stakeholder resources toward addressing key unmet medical need. Most children are healthy, and therefore, the number of children available to participate in medicinal product development research is limited, regardless of therapeutic area. Therefore, the CMWP believe that a more concerted effort should be made to identify and prioritize real and unmet paediatric needs to better guide stakeholders in prioritizing their resources and working with basic researchers to drive innovation where it is truly needed and can be impactful. By refocusing the energy of all of the stakeholders on need, there will be greater availability of limited resources to facilitate paediatric medicinal product development.

More multi-stakeholder efforts and resources must be invested in activities supporting collaborative basic paediatric research to establish the scientific basis for medicine development. Some important activities have already been started under IMI or through other consortia, such as EUPFI or Transcelerate Biopharma .

The design and execution of the clinical trials in paediatric development plans requires the availability of a well-funded clinical research infrastructure. More resources are required from the EU and at Member State level to create sustainable cross-regional clinical trial networks that can advise on meaningful programs for product development and deliver high quality data in a timely manner to swiftly progress marketing authorization applications for new paediatric medicines.

The new clinical trials Regulation that will come into application in Europe in 2018 will certainly help improving the harmonization of requirements across countries to facilitate the clinical trial approval process. However opportunities for more multi-stakeholder collaboration should be established to harmonise best practice and eliminate administrative, legal and operational hurdles at the clinical trial investigation site which may currently cause delay in starting the actual enrollment of patients.

The CMWP also believes that there is significant work to be done in regards to ‘accessibility’. We believe that there has been tremendous emphasis placed on stakeholders to engage on design, implementation and completion of paediatric product development plans, and limited (no) emphasis placed on ensuring that paediatric indications that result from these programs (e.g., market authorisation of the paediatric indication or formulation) are being made available by payors or formulary considerations at the Member State level. Therefore, we believe that there is a valuable role for a HTA at the time a PIP application to provide input into whether or not future paediatric indications would be reimbursed and whether resources should be applied for its’ development. If a patient will never be able to access the therapy once approved, should stakeholders be compelled to commit significant resource to conducting or participating in a paediatric program.

- “ ... to ensure that medicinal products used to treat the paediatric population are subject to ethical research of high quality and are appropriately authorized for use in the paediatric population, ...”

The CMWP believes that there is sufficient evidence to support an improvement in the overall quality (e.g., robustness of sample, appropriateness of endpoints) of paediatric medicinal product programs that are being proposed and agreed since the entry into force of the Paediatric Regulation. We are concerned there are many studies that have been agreed under the Regulation where the odds of completion are very low (e.g., DM Type II, melanoma). It is unethical to start a study that has a low (no) probability of completion or low (no) likelihood of yielding a meaningful conclusion. As previously mentioned, paediatric patients are a precious resource - it is rare that robustly-powered confirmatory studies can be completed, especially when numerous competitive programs are running

in parallel. Feasibility studies and their role in determining whether or not a study can be completed should have a more prominent role in the consideration of whether or not a paediatric program should be required under the Regulation.

We are encouraged by the evolution of thinking on alternative approaches to data generation (e.g., use of pharmacometrics, extrapolation, alternative trial design) that make smarter use of existing data to inform on program design. We applaud the EMA in its' contribution to the ICHE-11 addendum which promotes these concepts to be considered not just in Europe, but globally across regional health authorities. To this end, however, we are concerned that there is not enough opportunity for stakeholders to maximize regulatory pathways to ensure convergence of opinion both within the EMA (e.g., across the PDCO and CHMP, SAWP, and COMP) and between agencies (e.g., EMA and FDA). It is not the experience of our membership that there has been enough done on the implementation end to facilitate a more facile and efficient process to agreeing a paediatric program that can meet the needs of each regional authority.

- “...and to improve the information available on the use of medicinal products in the various paediatric populations.”

The CMWP believes that the Regulation has facilitated many means of ensuring that information on medicinal products is available. As previously noted, there is evidence that there has been an increase in the number of new paediatric indications for products approved through the centralized procedure which is a win for the paediatric population. We encourage the EMA and national Health Authorities to do more to facilitate a broader knowledge of the availability of this information amongst healthcare providers. There has been no analysis provided to assess whether the new paediatric indications resulting from the Paediatric Regulation are changing practice habits or, whether or not the new paediatric indications have led to a decrease in off-label use in paediatric patients in the EU diagnosed with the indication. We believe that the Paediatric Regulation has an opportunity to positively influence a change in practice habits and subsequently patient outcomes.

- “... achieved without subjecting the paediatric population to unnecessary clinical trials ...”

As previously discussed, the CMWP believes that there is an opportunity to utilize alternative approaches to data generation that will reduce the overall number of paediatric patients necessary to be studied during the development program. Use of pragmatic approaches grounded in existing knowledge of the disease will better facilitate an efficient development program for paediatric patients, thus reducing unnecessary studies. Further, we believe that there needs to be a more concentrated effort to evaluate paediatric patients (e.g., adolescents) as part of the adult development program when pathophysiology of disease, progression of disease, and underlying physiologies allow. To facilitate this, there is opportunity to better implement an efficient process to align the recommendations within the EMA on the acceptability of paediatric program by the PDCO and CHMP.

Many of the paediatric diseases being studied as part of a medicinal product development program meet the regulatory definition for orphan. Further, many paediatric programs have access to only a minimum of paediatric patients that meet eligibility requirements for a study. Therefore, a global approach is essential for any paediatric development. The CMWP believes that more must be done to facilitate a multi-regional regulatory pathway to better converge regional positions and reduce the potential for multiple studies in the same paediatric population. While the Common Commentary is an important forum for regulators to discuss common paediatric topics, a separate paediatric parallel advice procedure that allows industry participation could be considered to enhance a common understanding of key program elements and potentially efficiency.

- “...and without delaying the authorisation of medicinal products for other age populations.”

The CMWP believes that the Regulation does not contain any provisions that overtly impact the timeline for authorisation of medicinal products for other age populations. However, acknowledging that this could occur in theory, we encourage flexibility and pragmatism should such an issue arise. Resource allocation for development programs within available R&D resources may lead to decisions that may have an indirect impact on the priority and speed with which other development programs can be executed.

In closing, the CMWP is encouraged by the commitment to improve paediatric patient outcomes through a myriad of resource investments across our membership. We believe that there has been positive change in Europe as a result of the Regulation, and we acknowledge that problems still remain. We have mentioned the critically important aspect of prioritizing paediatric patient need, and have offered suggestions on how that may be addressed through a more pragmatic implementation. Our membership also believes that there is a need to highlight that our stakeholder groups cannot bear the full weight of responsibility to address these paediatric needs. Societally, there needs to be a greater commitment and investment in building a sustainable paediatric research infrastructure. Investigating the benefit and risk of a medicinal product in the paediatric population requires investments in basic science research and paediatric disease models. Teaching institutions must be adequately funded to educate young trainees on the value of paediatric research and paediatric drug development research. Societally, there needs to be a greater emphasis on protecting children through research and not from research. All of this, taken together, will vastly improve the environment within which the stakeholders represented by the CMWP are able to deliver on the aims of the Paediatric Regulation.

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?

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?

