

ESDP European Society for Developmental Perinatal and  
Paediatric Pharmacology VZW  
Dienst Neonatologie  
Herestraat 49,  
3000 Leuven  
Belgium

To  
**Nathalie Macle**  
**Stakeholders and Communication Division**  
European Medicines Agency  
30 Churchill Place  
London, E14 5EU  
United Kingdom

**Re: 'PCPM/16 — Paediatric Report'**

19.2.2017

Dear Mrs Macle,

Please find enclosed comments to your public consultation "PCPM/16 — Paediatric Report" by the ESDP European Society for Developmental Perinatal and Paediatric Pharmacology VZW.

Sincerely,

Stephanie Läer

Prof. Dr. Stephanie Läer  
Secretary General ESDP  
Institute of Clinical Pharmacy and Pharmacotherapy  
Heinrich-Heine Universitaet Duesseldorf  
Universitaetsstrasse 1  
40225 Duesseldorf, Germany  
Email: [Stephanie.laeer@uni-duesseldorf.de](mailto:Stephanie.laeer@uni-duesseldorf.de)

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

Yes, we do agree that specific legislation supporting the development of paediatric medicines is necessary to guarantee evidence-based paediatric medicines.

**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?

Respectable progress has been made since the Paediatric Regulation was adopted in 2007. Therapeutic areas like juvenile rheumatoid arthritis, haemangiomas, and pulmonary hypertension have benefitted from new medicines. Supported by public funding, academics have initiated and performed substantial work for some of these therapeutic areas. Several researchers have noted that the starting point for paediatric investigation plans is often a research and development program for adults, and thus many unique health problems and diseases in the paediatric population are not (a priori) considered. In addition, the needs for subpopulations with major co-morbidities (e.g. ICU patients, obesity) are not considered because these patients are regularly not recruited due to exclusion criteria.

**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 Have existing treatments been replaced by new licensed treatments?

Whether or not new treatments have replaced older ones depends highly on the country and on how insurance companies reimburse health care facilities for the treatments. In some countries, off-patent treatments prepared as extemporaneous formulations are cheaper than newly authorised paediatric medicines. In these cases, the cheaper treatments are preferred.

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

Pharmaceutical companies are asking ESDP members to contribute to the development of paediatric medicines as external consultants. Other evidence has shown that large companies have more resources to get paediatric studies done as compared to the small ones. Therefore, it might be worthwhile to take into consideration which companies might need support to get the appropriate studies done. Other evidence has shown that a pharmaceutical company may decide to discontinue its adult development program for any reason. The need to continue the paediatric program has to be addressed accordingly.

**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 comments for that; it is assumed that in general it does.

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

The orphan designation is an important part of the Paediatric Regulation. For years to come, the EMA might consider allowing companies to apply for one of the two award pathways based on companies assessment.

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

It is appreciated that efforts have been made to learn from the first-year experience and to simplify the PIP negotiation process. However, there needs to be awareness that other problems still arise and need attention—e.g., issues related to full-blown PIPs for very rare diseases might be not get fulfilled if several companies have PIPs for the same disease. Concerning the integration of adolescents into adult trials, several aspects need to be considered. Adolescence is a very unique, vulnerable, and challenging stage of development that is characterised by a period of final growth, reproductive maturation, and cerebral remodelling (Seyberth & Kauffman, 2011). Moreover, depending on the state of puberty, patients between the ages of 12 and 17 are still at a different developmental stage. That is why we cannot easily lump together adolescent patients with adults. There are only certain exceptions, such as those outlined in the EMA/PDCO Standard Paediatric Investigation for Allergen Products for Specific Immunotherapy. When using the concept of extrapolation by modelling and simulation with the intention of reducing the number of study subjects, we should always be aware that we have not disclosed all of the unforeseen changes during maturation, nor do we have the appropriate parameters or biomarkers for these developmental changes that need to be considered for modelling and simulation. Thus, there are certainly some limitations for these concept. However, close collaboration will help to solve some of the problems.

**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?

Regarding the regulatory aspect, the present waiver concept is quite straightforward. In addition to a fixed 'mechanism of action' mentioned above, paediatric drug development follows a moving target throughout the maturation process. So, before coming to any final decision about granting an exemption (a waiver), one should be familiar not only with a single medicine's mechanism of action but also with the medicine's mechanism as a moving target throughout paediatric development.

Limitations of the waiver concept have been noted such as missed indications—e.g., concerning the COX-2 selective inhibitor celecoxib (a NSAID with less adverse gastrointestinal drug reaction), which is primarily indicated for the treatment of patients with osteoarthritis, a degenerative disease of the joints. In children, there might also be an indication for this drug to treat preterm infants with either symptomatic patent ductus arteriosus or life-threatening renal salt and water wasting (antenatal Bartter syndrome). In both (neonatal) diseases, increased prostaglandin synthesis is involved in the pathophysiology, as it is in osteoarthritis of the elderly. Another example might be sildenafil for erectile dysfunction in adult males. This drug has been shown to be very helpful and actually life-saving in newborns with pulmonary hypertension. It might be considered appropriate to have an opportunity to go back to the company afterwards and explain to them that new data have resulted in a need to study their product in kids as well.

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

We do agree.

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

We are aware of the 'written request' procedure in U.S. legislation, as it creates an opportunity to follow an urgent paediatric (therapeutic) need.

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

We support this view and agree with the content. In the above-mentioned case, the obligation to transfer the marketing authorisation to another company is fully justified. Otherwise, if the company is not cooperative and withholds the marketing authorisation, the agency may consider appropriate to make this behaviour public.

**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?

We think that the concept of PUMA is appropriate and that the main goal of PUMA remains absolutely worthy. However, the EMA and the national agencies should educate the national health officials about this problem/issue, which cannot be solved by the EMA alone. Often, health insurance companies refuse to pay for PUMA medicine, which is more expensive than generic medicine prescribed off-label. However, it could be also counterproductive if pharmaceutical companies go into the market with excessively high prices (e.g., inhaled nitric oxide [iNO] for persistent pulmonary hypertension of the newborn [PPHN] or propranolol for infantile haemangioma). Therefore, the EMA should search together with companies from the pharmaceutical industry for more attractive incentives or awards. In addition, there is still a need for additional public funding with a reevaluated and optimised support structure. FP7 projects can be regarded as a learning curve for public funding concerning PUMAs, as many of FP7 projects failed due to the difficulties of small businesses to provide adequate paediatric formulations.

**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?

There is an absolute need for oversight by an independent ethics review committee to ensure that kids are not becoming harassed too many studies that go on for too many years before reaching completion. Furthermore, multiple companies should avoid simultaneously carrying out trials with children for the same adult disease, especially when there is no urgent paediatric need (e.g., type II diabetes). If pharmaceutical companies are not willing to collaborate with each other, then the benefits/rewards of the Paediatric Regulation should (if possible) be granted only to one company. Any innovative approaches of the PDCO to prioritise which medicine should be developed in children, as outlined in the 10-year report, are certainly appreciated.

**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?

We assume that, in the long run, the proper functioning of the system is impacted, as it is expensive to provide highly qualified people for the EMA/PDCO. Therefore, companies should have to contribute to this service by paying.

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

The Paediatric Regulation has had no direct impact on paediatric research. However, the Paediatric Regulation has raised awareness of the process of product development and its associated regulatory affairs. More clinical drug trials have been conducted. The Regulation has certainly increased our awareness of some gaps in our knowledge of maturation processes and of the pathophysiology of diseases at quite different stages of paediatric development. Therefore, besides the implementation of the Regulation, academic teaching and training should focus much more on maturation processes and paediatric physiology.

It is therefore mandatory to find ways of funding clinical research infrastructure using public and private sources as has been done for IMI2 funding. Larger pharmaceutical companies have realised this across the globe and are pushing for the development of a global network. The best-case scenario would be to have a global network with more collaboration between the EMA and the FDA. This is more necessary than before, because the regulatory hurdles have increased in order for academics to proceed with investigator-driven studies aimed at identifying new indications in the paediatric population for drugs that have already been approved for the adult population or for different age classes in the paediatric population.

**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?

It is quite reasonable to believe that precision medicine, which is based on patients' individual genes, may in the future be more important in paediatric pharmacotherapy, particularly in paediatric oncology. However, we believe that for the time being, and also in the near future, the dynamics of maturation remains the most dominant factor. Thus, the younger the patients are, the more influential the developmental aspects (and not so much the genetic aspects) will be on personalised pharmacotherapy.

**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?

We think that the implementation of the Regulation has made an important difference. The next steps for facilitating paediatric research and drug trials will be to perform age-specific and appropriate clinical investigations and to determine age- and disease-specific adverse events and biomarkers. These steps must be taken to ensure the development of safe and effective medicines for kids across the world. Additionally, programmes in paediatric clinical pharmacology for scientists and physicians are mandatory to foster substantial progress in the field of paediatric research and drug trials.

We would like to give the original comment of one of our members (Hannsörg Seyberth, Germany) who had been involved in the discussion of the Paediatric Regulation formation in 2007 concerning this item.

*"My personal expectation of this piece of legislation or better of the global initiative of "Better Medicines for Children" is or at least was that sooner or later we will come up with an overall saver and more innovative drug treatment for children. Achieving this objective involves, on the one hand, taking full advantage from the know-how and the infrastructure that has been developed during the implementation of the Paediatric Regulation and on the other hand, all the potential arising from the expansion and knowledge of modern medical sciences and methodology that enables us to conduct studies in vulnerable patient populations that had not been impossible and/or unethical in the past. However, at the same time as economic pressure on the medical staff has significantly been increased, an enormous burden of bureaucracy and regulation has markedly grown in clinical research, which unfortunately also does affect the essential pilot and Proof-of-Concept studies. Moreover, rarely young physicians have had a sound preclinical training in basic science, such as in (molecular) physiology/pharmacology or biochemistry that enables them to develop their one clinical research projects. This ability also might include the skills to detect and identify still existing gaps in our current knowledge about old, off-patent medicines. With this qualification they should also be able to provide the basics for extrapolation and simulation as well as to develop the essential biomarkers and endpoints to conduct paediatric studies.*

*Therefore, this comprehensive qualification needs to be fostered by training the next generation of paediatricians. However, unfortunately the young colleagues often have just passed some GCP-courses or at the best training course on the paediatric regulation that qualify them to be a useful "medical technician" for pharmaceutical companies on the ward or in the clinics. Hopefully, the GRiP Network of Excellence with its master program in paediatric clinical pharmacology will provide a deeper knowledge in the basics and dynamics of paediatric pharmacology (on an international level). However, also here we need highly qualified academic lectures and teachers with clinical expertise. They will probably not come from Industry.*

*Why not getting started on an ambitious MD-PhD-programme right now or as soon as possible, preferable with the focus on paediatric pharmacology, to generate a sufficient number of independently thinking and working physician scientists, who later should have a chance to enter in an academic tenure track programme in clinical research institutions or academic hospitals?"*