



Contribution regarding Public consultation on the revision of
"**COMMISSION REPORT ON THE PAEDIATRIC REGULATION**"
'PCPM/16 — Paediatric Report'.

This contribution letter represents:

- Medicines Committee of the Spanish Pediatrician Association (CM-AEP).
- Translational Research Network in Pediatric Infectious Diseases (RITIP)
- La Paz Central Research and Clinical Trials Unit (HULP-UCICEC).
- Clinical Trials Unit -Hospital Clinico Universitario de Santiago – Instituto de Investigación Sanitaria de Santiago.
- Spanish Paediatric Clinical Trials Network (RECLIP).

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

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

We agree with the need for Paediatric Regulation although it is just only one of the measures that could improve the availability of evidence-based paediatric medicines.

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

Although the Paediatric Regulation could have had some effects in some therapeutic areas, these have been mainly in medicines that have interest for adults, and when cost effectiveness is guaranteed.

Many pediatric disorders do not entail significant economic gains, including those not exclusive of children such as infectious diseases (ie: tuberculosis) as well as for instance many antibiotics do not have adequate pediatric formulations.

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 Have existing treatments been replaced by new licensed treatments?

In general not significantly, maybe in some therapeutics areas or class of medicines (oncology, biologic agents mainly).

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

Probably, the costs of the paediatric investigations plan could be acceptable for pharmaceutical companies, or not excessive, if it is contained within the levels mentioned in the report. Nevertheless, one of the most common problems could be the post-approval situation. If the pharmaceutical company does not get a profitable price to sell the product, in the different countries, all the effort previously done will not have been worth it. A reward as the SPC protection extension might become negligible when it is linked to the commercialization in all member states. Some member States will only authorise commercialization at a regulated price (for reimbursement) not allowing a commercialization at free price outside reimbursement.

Delays in the approval of the adult indication due to the paediatric programme if they have to be carried out simultaneously might be a significant hidden cost. Deferrals cannot always be used.

As long as local Regulatory Agencies and Governments in EU member states are not committed to favouring adequate prices for medicines and pediatric formulations, pharmaceutical companies will not be interested in pediatric research. National competencies in pricing and regulation are quite exceptional within the single market and compromise the effectiveness of European legislation.

The risk/benefit profile for the companies is not only driven by benefit. Paediatric research implies a greater risk of failure due to clinical research carried out in a difficult and probably frailer population. A safety concern in

children might affect the adult indication even if the SPC is not changed or withdrawn.

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?

Pharmaceutical companies should have to answer this question.

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

Again, involved companies could have a better informed opinion.

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

Although a long way is still ahead, the Regulation's implementation probably has improved or solved some problems. However, as the report recognised, the legislation fails to establish a commercial incentive for the development of paediatric medicines and focuses on regulation and incentives that are not always clear. In this situation paediatric population will always be at a disadvantage compared to the adult population. On top of this, increased cost might have the undesired effect of making economically not viable development of medications for adults having a direct impact on such population as well as on the traditional "off-label" use.

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?

Waivers: we have not specific comments.

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

We agree

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

Voluntary investigations plans: no comments.

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

We consider especially important to protect children, with regulation about biosimilar products. Up to what extent this is achieved

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 agree with the idea that PUMA concept has been useless. In our opinion, the low price in the market of these off-patent medicines is one of the most important problems.

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 consider that all efforts must be conducted to convince stakeholders to engage in collaborative research, promoting clinical trials networks that provide high quality research in children. But collaborative research for different medicines within the same therapeutic class is wishful thinking since companies use different products to compete among them, and this is as a consequence, benefiting the patients with a wider choice of drugs.

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?

EMA should evaluate the possibility of reimbursing national experts for doing this work. Advice must not be free, because there is not an unlimited supply of qualified professionals willing to give advice without been paid for a prolonged amount of time. Directly converting these costs into fees to the industry would be contradictory with a system with rewards.

Every decision should lead to a sustainable system, and increased costs will always be, long term, passed, either directly or indirectly, onto the users. These increased costs will be paid by the individuals or the public/private insurance systems.

Sustainability is difficult to achieve based only increased research without working on more efficient research (also for adults), more efficient regulatory processes (local pricing might be relevant although difficult to manage, but local approvals etc. are questionable). All regulations tend to increase the cost of research and it is naïve to think that this will not be passed in one or another way to the users.

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

Paediatric Regulation is necessary without any doubt and IMI public-private partnership ('innovative medicines initiative') should facilitate the establishment of an EU paediatric clinical trial network.

Considering questions 14 and 15 separately is, however, nonsensical.

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?

We need a regulation that covers the near future of pediatric clinical research, giving adequate support and/or reinforces the use of adaptive trial design, immediate data transfer to safety monitoring committees, risk-based monitoring, or near real-time dose adjustments. Linked to this, data integration and visualization are changing the clinical trials landscape, and specific advice/rules should be warranted.

Adaptive design trials, and even perpetual adaptive design trials, are gaining interest in other disciplines, particularly when the entity has low incidence and/or recruitment is particularly difficult, allowing flexible and real-time analysis of F2F comparison of several compounds. It can be the breakthrough strategy to rapidly assess old and new interventions for emerging diseases. The regulatory support for this scenario is unclear in the EU and this prevents pharma and investigators for a wider use of this strategy. Furthermore, where several molecules with a similar TPP compete in the same scenario, this kind of design would be more efficient and also might prevent unnecessary exposure of children to investigational drugs.

Personalized Medicine, although a complex and multifaceted construct, is becoming increasingly part of the trials themselves. Selective selection of participants in pediatric trials based on genomic or proteomic biomarkers - let's call them genomic or proteomic inclusion criteria- needs a proper regulation coverage. In practice, and for the setting of pediatric clinical trials, personalized medicine is particularly interesting in the short term for individualized data assessment and combination trials.

For all these future scenarios, we need to adapt all the usual procedures, from electronic ICF signature, centralized and fast-track EC approvals and real-time super-specialized EC to address all the issues of these breakthrough studies, to ensure a top-to-bottom strategy that normalizes and guarantees common procedures and prevents the addition of nonsense-superfluous local/national requisites. We need a strong European directive that overcomes the local-national hurdles for pediatric clinical research.

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?

In summary, this entire project is based on the development of new products and new paediatric drugs, but nobody deals with the existing ones,

which are the majority and providing adequate paediatric formulations, or having the paediatric indication for drugs that are already authorized for adults long time ago. Existing drugs that are available in paediatric presentations often have ridiculous prices (antibiotics for example) and companies just want to remove them, so we are constantly faced with shortages and supply problems.

Independent research carried out without private support, should be promoted in order to cover areas with no commercial interest.

This whole plan is praiseworthy, and surely in the future will improve the situation of the children, but many other measures are necessary.