THE 2017 COMMISSION REPORT ON THE PAEDIATRIC REGULATION – CONSULTATION RESPONSE

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Replying as: Two separate healthcare professional organisations
Please indicate the level at which your organisation is active: National

Section 1. General feedback on Paediatric Regulation	
General comments on the original impact of the 2006 Paediatric Regulation	The legislation has raised awareness in the pharmaceutical industry about the need for investigation into all relevant medications, in children of all ages, within the medicine development process.
Potential amendments that should be made to the 2006 Paediatric Regulation	There is a need for a more robust process for older, off patent, medicines for which no Paediatric data exist. This should be through further research by academia (with significant support, possibly augmented by a fund established for this purpose), if changes to legislation are unable to strengthen the PUMA process to make it more effective.

Section 2. Feedback based on 10-year report to European Commission		
Consultation item no.	**Statement ref.**	**Feedback**
1. Do you agree that specific legislation supporting the development of paediatric medicines is necessary to guarantee evidence-based paediatric medicines?	More medicines for children	Yes, supportive legislation has been a huge step forward in making sure new medicines are available with robust age-appropriate dosing information and formulations.

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?	Mirroring paediatric needs	The disease areas where there is no adult pipeline is an important issue for paediatrics. Ultimately funding for research and development in areas without, or with minimal adult indication, will depend on market need and funding from companies. We believe the Commission can enhance research in these areas and achieve important child benefit by funding through IMI or similar mechanisms. New paediatric treatments have become available in cardiovascular disease, pain relief and other areas and there may be new paediatric medications to come in other areas such as diabetes mellitus type 2, and antibiotics for infectious diseases, that would have adult benefit.
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?	Availability of paediatric medicines in the EU	From a UK perspective there are limited examples of an increase in medications available for children over the last 10 years and existing treatments replaced by new licensed treatments.
4. Do you have any comments on the costs for pharmaceutical companies to comply with an agreed paediatric investigation plan?	Reasonable costs	The research costs appear small in the big scheme of R&D spend by companies. However, the timing of this spend can cause problems for companies, as each R&D spend is assessed utilising an NPV calculation. Therefore, if the return on investment is lower than spend, the costs and additional benefit can be seen as cumbersome and bureaucratic by companies. A grading scale of regulatory fees for submission may help in encouraging smaller companies to file for a Paediatric license and carry out the research. At a practical level, there should be more focus from both sides on the feasibility of studies at the stage of initial submission of PIPs, as this would decrease costs.
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?	Functioning reward system	This does seem to be a reasonable process, allowing companies the opportunity to gain additional revenue if they are organised in performing child health research. It may help to allow further time points at which PIPs could be discussed later in the process. Also, in some cases the reward may be far more than the costs. Generally, companies calculate the cost per project/product as a single NPV. Therefore, even if the same company is undertaking PIP for several products, the ones with the highest rewards are likely to get the most attention. A reward system at a company level, as opposed to a single project/product level, could be considered by the regulation, however this may be hard to implement.
6. How do you judge the importance of the orphan reward compared to the SPC reward?	The orphan reward	The report describes the situation well, with companies likely to continue to use whichever reward is most financially beneficial for them. With the advent of precision medicine, it may be that the rules for orphan designation will need to be reviewed.

7. Do you agree that the Regulation's implementation has improved over time and that some early problems have been solved?	Improved implementation	Strengthening of links between EMA and FDA in drug development is essential, this can prevent duplication of studies that lead to more children needing to be recruited (as studies are duplicated in both jurisdictions) due to differing regulatory requirements/study methodologies being recommended. In most instances, development plans are driven by FDA requirements due to the size of the market, and the fact that many R&D headquarters are based in the US. Therefore, reflection of EMA requirements by the FDA, and vice versa, will help companies to anticipate requirements in the different jurisdictions more successfully.
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 and the 'mechanism of action' principle	This question mainly deals with the appropriateness of waivers. However, the conduct of paediatric diseases, and the sample size to meet the requirements, are sometimes in direct conflict with the registration. This may also play a role in some of the companies deciding to use waivers and some voluntarily conducting studies. Therefore, the regulation needs to be careful to not reduce innovation/ licensing of medicines for the population at need. Where companies voluntarily investigate use of oncology drugs in different indications in children, because they see an opportunity, there should be an emphasis on feasibility. Also, in cases where there are only small numbers of children, a different way of obtaining evidence may be more appropriate than a clinical trial e.g. a registry study, or a carefully designed observational cohort.
9. Do you agree the above assessment of deferrals?	Deferrals	There must be a balance between ensuring no delays to adult development and no unnecessary delays to paediatric studies.
10. Do you have any comments on the above?	Voluntary paediatric investigation plans	This could be highlighted more to companies (with examples to illustrate the benefits).
11. Do you have any comments on the above?	Biosimilars	A complex area, as they drive down cost overall but could lead to off label use of biosimilar, when no paediatric data is available for the product. Also, if they don't produce the Paediatric formulation then we may be asked to use a different medication, if originator product costs are high.
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?	PUMA — Paediatric-use marketing authorisation	This has been a disappointing area that has not led to the advances hoped for children. Only 3 have been issued, showing it is not attractive to industry. Funding through schemes such as the EU FP7 programme, when primarily lead by multinational academic institutions (in partnership with small Pharmaceutical Company Partners) have struggled, often delayed by difficulties in negotiating both the PIP systems and the need for getting multiple countries legislative and ethics approvals for the projects. Detailed consultation with UK paediatric associations (such as the Royal College of Paediatrics and Child Health; the Academic Paediatrics Association of Great Britain and Ireland; the Neonatal Society; the National Institute of Child Health Neonatal and Paediatrics Clinical Studies Groups) may help to revise current regulation to be more attuned to child needs.

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?	Scientifically valid and ethically sound — Clinical trials with children	The legislation has led to awareness around trial methodologies in children, such as the increased use of PK Modelling for dose regimens in neonates and children. The increased awareness and profile of studies has stimulated guidance updates from RCPCH (Modi N, Vohra J, Preston J, Elliott C, Van't Hoff W, Coad J, Gibson F, Partridge L, Brierley J, Larcher V, Greenough A, for a Working Party of the Royal College of Paediatrics and Child Health Guidance on clinical research involving infants, children and young people: an update for researchers and research ethics committees Arch Dis Child 2014; 99(10):887-91), and prompted the Nuffield Council on Bioethics to produce a report on Children and Clinical Research (2015). Awareness regarding the involvement of children and their families, early in the planning of a trial, has risen and become accepted with the establishment of children and young people advisory groups (see RCPCH Infants', Children's and Young People's Child Health Research Charter 2017). This has also been addressed through the establishment of networks (e.g. National Institute for Health Research Children Network) and databases (e.g. Imperial College London National Neonatal Research Database) supporting research where some aspects of studies can be conducted in a non-competitive framework, and some as discrete studies.
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?	The question of financial sustainability	A free of charge system is very helpful to those academic institutions involved, and it encourages submissions in general. PIPs should remain free, and perhaps consideration should be given to other paediatric specific documents, such as paediatric RMPs, to further boost submission. However, we acknowledge that this system may be difficult to maintain as it relies on the good will of its expert members, which in a busy NHS in the UK is becoming increasingly difficult. One suggestion could be to identify funding from other streams (within EMA) to continue to do the work, but with a smaller contribution towards the continuation of the system. There is also a need for the continued education and development of those with expertise to work within industry, regulatory bodies, professional organisations, and academia to support and carry out studies.
15. How do you judge the effects of the Paediatric Regulation on paediatric research?	Positive impact on paediatric research in Europe	The UK was ahead of many member states in establishing a Medicines for Children research network. Some infrastructure has struggled recently, for example with establishing an EU wide network for children, and has a long way to go. However, the IMI is a good next step.

16. Are there any emerging trends that may have an impact on the development of paediatric medicines and the relevance of the Paediatric Regulation?	"Mirror, mirror on the wall" - Emerging trends and the future of paediatric medicines	Greater emphasis might usefully be placed on real world evidence in paediatric patients, for example, trial designs where post marketing off label use in children, collected in registries or held in databases of routinely recorded information, can be used to obtain regulatory meaningful evidence to support label extensions, and conduct more efficient clinical trials (e.g. Gale C, Hyde MJ, Modi N on behalf of the WHEAT trial development group Research Ethics Committee decision making in relation to little-used methods for efficient trial design Arch Dis Child Fetal Neonatal Ed. 2016 Sep 14 [Epub ahead of print]) The Critical Path International Neonatal Consortium is an example of collaboration between industry, academia, parents, and clinicians, to speed the path of neonatal drug development. There are now three gene based medicinal products that have recently been granted marketing authorisation by the EMA, of which two are indicated for the treatment of genetic diseases in children. The development process for gene therapy based products is different to that of products which are new chemical entities. The diseases being treated caused by specific gene mutations with gene therapy are typically identified in early childhood and hence need treatments at this stage in life. As more cell and gene based therapies are in the development pipelines of companies, it is important that future Paediatric Regulations take these new treatment modalities into account.
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?	Other issues to be considered	The regulation reflects unfulfilled expectations around PUMAs. There is disappointment around the need to further incentivise studies to obtain evidence for older medicines often used in children.