

Brussels, 20 February 2017

Dear Sir/Madam,

european association of  
hospital pharmacists

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**REMARKS FROM THE EUROPEAN ASSOCIATION OF HOSPITAL PHARMACISTS (EAHP) ON THE EUROPEAN COMMISSION'S PUBLIC CONSULTATION ON THE OPERATION OF THE PAEDIATRIC REGULATION**

The European Association of Hospital Pharmacists (EAHP) supports the intent and the achievements to date of Regulation 1901/2006 ('The Paediatric Regulation') and offers the below remarks in response to a public consultation in a spirit of assisting the Regulation's continuous improvement.

Below are the key remarks of EAHP in short summary.

***1. The EU must remain bold in asserting society's needs in medicines development***

The success of the Paediatric Regulation is a demonstration of the benefit achieved when European Governments unite to make clear to the medicines sector the needs it expects the research community to address, and puts in place a framework of incentives and obligations to support this. Useful lessons may therefore be taken for other areas of current need such as antibiotic development and geriatric medicine.

***2. Keep all regulations pertaining to medicines development under review and seek a joined up and holistic response***

The European Commission should understand the need to keep under consideration the operation of medicines regulation in Europe, and therefore conduct the review of the Paediatric Regulation within a context of other regulations that might be updated, such as those for orphan medicine and the community code relating to medicinal products for human use, both of which also impact the paediatric medicine environment. We encourage the Commission to bold in imagining all opportunities for improvement.

***3. Improve the participation of healthcare professionals in EMA's Paediatric Committee***

The terms of membership for healthcare professionals in the EMA Paediatric Committee require improvement. As currently constituted Committee membership is highly impractical, in terms of time commitment and compensation, for busy healthcare professionals at the coal-face of paediatric treatment. Healthcare professionals wishing to assist the work of the Paediatric Committee should not be expected to be financially

worse-off as a result of the time commitments associated with Committee membership and participation.

#### **4. Go global in approach!**

The opportunity of 10 years' operation of the Regulation should be utilised to now heighten the EU's international outreach on paediatric medicine development. Opportunities for greater cooperation and potential harmonisation of paediatric medicine regulation at the global level should be identified and pursued. Paediatric medicine development is not an inter-country competition, but rather an international effort to meet unmet need. Regulatory improvement endeavours should reflect this.

EAHP, and its network of hospital pharmacist associations across 35 European countries, remain at your disposal for any further information, assistance and advice that can be usefully transmitted to assist the Commission and national governments in this policy domain.

Yours sincerely,

Joan Peppard  
President  
European Association of Hospital Pharmacists (EAHP)

### **RESPONSES TO CONSULTATION QUESTIONS**

**Q1. DO YOU AGREE THAT SPECIFIC LEGISLATION SUPPORTING THE DEVELOPMENT OF PAEDIATRIC MEDICINE IS NECESSARY TO GUARANTEE EVIDENCE BASED PAEDIATRIC MEDICINES?**

Yes. The 2007 Regulation meets an important need to incentivise and indeed mandate developers of medicine to consider paediatric use. Its success should now be built on with such improvements as:

- Increasing the participation of healthcare professionals in EMA's Paediatric Committee by improving the terms of membership;
- Making greater global outreach for purposes of coordination and potential harmonisation of regulatory requirements in the area of paediatric medicine development;
- Improving the transparency and accessibility to information about past trials and paediatric medicines development activity

- Exploring how *other* EU legal instruments governing medicines development and use could be improved in respect to their impact on paediatric medicine (e.g. orphan medicine regulation and the EU community code on relating to medicinal products for human use).

We also urge that further and specific focus be given to answering the question of how to incentivise research activity in respect to:

- Disease conditions *only* presented in children;
- Use of off-patent medicines for paediatric use; and,
- Off-label use of medicines in neonates and children.

**Q2. 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?**

EAHP highlight to the European Commission that whilst the Orphan Medicines Regulation has brought about a slew of important new treatments for rare metabolic diseases (e.g. Aldurazyme, Carbaglu, Cerdelga, Cystadane, Elapraxe, Fabrazyme, Kuvan, Myozyme, Naglazyme, Orfadin, Procysbi, Replagal, Soliris, Vimizim, Vpriv and Zavesca), it stands out that only one orphan drug designated for the use in children with cancer without passing first by an adult indication (Unituxin). Achieving improvement in this regard should be a matter of attention within the European Commission's review of the Paediatric Regulation, and underlines our recommendation that the review be conducted with a firm eye also on the operation (and scope for improvement) of *other* regulations in the medicines development sphere.

**Q3. 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?**

The Commission should have an awareness that several existing treatments used off-label and several compounding formulations (magistral or officinal) have been replaced by licensed treatments as "orphan drugs" for children: Busilvex, Cayston, Cystadane, Granupas, Kolbam, Orphacol, Pedeaa, Peyona, Procysbi, Revatio, Siklos, Tobi, Votubia and Xaluprine.

This can lead to a scenario where the medicinal treatment therefore becomes more expensive to the health system, and so while an authorised medicine for paediatric use may exist, reimbursement may not. The net effect is therefore, perversely, *less* access.

This once more underlines an overall point EAHP makes in response to this consultation: review of the operation and areas for improvement in the paediatric regulation must be viewed alongside the operation of *other* EU legal instruments for medicines development that impact on paediatric medicine, such as orphan drugs legislation.

**Q4. DO YOU HAVE ANY COMMENTS ON THE COSTS FOR PHARMACEUTICAL COMPANIES TO COMPLY WITH AN AGREED PAEDIATRIC INVESTIGATION PLAN?**

In view of the ongoing strong profitability of the research-based pharmaceutical industry, and the benefits for meeting needs in respect to paediatric medicine, the costs of the paediatric regulation described in the consultation document appear entirely proportionate.

Moreover, the need to understand the levels of expenditure companies are investing in research as compared to other activities such as marketing need to be better understood by policy makers and the stakeholder community when evaluating the extent to which new forms of regulation on research might be considered. The consultation authors will no doubt be aware that skepticism exists in respect to quoted research and development costs<sup>1</sup>. A review of legislative tools that could be created at the EU level to improve transparency of pharmaceutical development R&D costs could therefore be a useful component of the Commission's review of the Paediatric Regulation. It could be highly insightful, for example, to know of the levels and percentages of R&D expenditure companies devote towards paediatric medicine. The publication of such data could also provide a further incentive for improvement. For example, one might imagine a soft incentive emerging from a corporate reputation perspective. i.e. being known as the company with the best record on investing in paediatric medicine development, and not to be known as the worst in this regard.

As a small aside, the consultation document describes the Paediatric Regulation as “an additional burden” for pharmaceutical companies. This seems a very subjectively laden description. A better form of description could be “regulatory expectation”. The expectation delivers strong public benefit. Whether the expectation can therefore be described as a ‘burden’ is debatable.

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<sup>1</sup> [www.ip-watch.org/2016/03/04/alleged-rd-costs-not-a-transparent-driver-of-drug-prices/](http://www.ip-watch.org/2016/03/04/alleged-rd-costs-not-a-transparent-driver-of-drug-prices/)

**Q5. DO YOU AGREE THAT THE REWARD SYSTEM GENERALLY FUNCTIONS WELL AND THAT EARLY, STRATEGIC PLANNING WILL USUALLY ENSURE THAT A COMPANY RECEIVES A REWARD?**

Yes, the evidence presented in the consultation document appears to suggest the reward system in generally functioning well and early strategic planning can help ensure a company receives a reward.

Presumably the forthcoming introduction of the European Unitary Patent System will also assist in this respect, by reducing workload with national patent offices.

**Q6. HOW DO YOU JUDGE THE IMPORTANCE OF THE ORPHAN REWARD COMPARED TO THE SPC REWARD?**

The description of the orphan reward within the consultation document underlines the need to view the development and evolution of the Paediatric Regulation in conjunction with that of other EU legislative instruments for medicines development, such as the orphan medicines regulation, and the EU community code relating to medicinal products for human use. EAHP urges a holistic review of all EU medicines regulation in order that opportunities for improvement can best be identified, and to mitigate against any risk of conflicting or contradictory initiatives.

On the matter of orphan medicines considerations, EAHP highlight to the European Commission that whilst the Orphan Medicines Regulation has brought about a slew of important new treatments for rare metabolic diseases (e.g. Aldurazyme, Carbaglu, Cerdelga, Cystadane, Elaprase, Fabrazyme, Kuvan, Myozyme, Naglazyme, Orfadin, Procysbi, Replagal, Soliris, Vimizim, Vpriv and Zavesca), it stands out that only one orphan drug designated for the use in children with cancer without passing first by an adult indication (Unituxin). Achieving improvement in this regard should be a matter of attention within the European Commission's review of the Paediatric Regulation, and underlines our recommendation that the review be conducted with a firm eye also on the operation (and scope for improvement) of *other* regulations in the medicines development sphere.

**Q7. DO YOU AGREE THAT THE REGULATION'S IMPLEMENTATION HAS IMPROVED OVER TIME AND THAT SOME EARLY PROBLEMS HAVE BEEN SOLVED?**

Yes, and this should be expected with the introduction of any new regulation. All regulation should continuously improve.

In respect to the consultation document's reference to 'assumptions and scare data', this underlines the overall need for emphasis to be placed on transparency and access to clinical trial data from past medicines development activity. While the 2014 Clinical Trials Regulation made some welcome advances in this respect there is still more that might be done in respect to data from trials conducted prior to 2014 and in respect to international harmonisation of transparency requirements. Both matters might be usefully considered by the Commission in the conduct of its review of the Paediatric Regulation. Greater transparency in respect to clinical trial results and international harmonisation of trial regulation can both assist the paediatric medicines development environment.

**WAIVERS AND THE MECHANISM OF ACTION PRINCIPLE**

**Q8. DO YOU HAVE ANY COMMENTS ON THE ABOVE? CAN YOU QUANTIFY AND QUALIFY**

The need to address the lack of development of medicines in conditions that are considered to present in children but not adults must be considered an urgent priority for the Commission's review of the Paediatric Regulation. Ways in which this could be addressed include by focusing attention on how the current research environment for academic clinical trials might be improved.

**DEFERRALS**

**Q9. DO YOU AGREE WITH THE ABOVE ASSESSMENT OF DEFERRALS?**

Whilst in some cases deferral of a paediatric investigation plan can be merited, it would seem against the logic of the Regulation that these be provided too readily. The criteria by which deferrals are granted could be a useful area for further review and consultation.

## **VOLUNTARY PAEDIATRIC INVESTIGATION PLANS**

### **Q10. DO YOU HAVE ANY COMMENTS ON THE ABOVE?**

The references to paediatric medicine regulation in the USA highlights the value in ensuring cooperation at the international level in respect to commonality in approach, in order that the strongest clarity, certainty and incentive can be provided to boost paediatric medicine research worldwide. Indeed, its possible that paediatric medicine may be a suitable area for EMA and FDA to consider conducting joint evaluation and authorisation.

Furthermore, if the USA's "written request" mechanism to stimulate research can be viewed as a successful mechanism, there's seems little reason why the approach might not also be adopted in the EU/EEA. This should be given active consideration during the Commission's review of the Paediatric Regulation.

As a further suggestion, EAHP emphasise to the Commission the value in enabling and facilitating not only large commercial organisations to conduct voluntary paediatric investigation plans, but also patient organisations, healthcare professionals, hospitals, and other 'non-traditional' leaders of medicines research. This is an important future trend for the Commission to reflect upon in the context of reviewing paediatric medicines regulation in the EU and suggests further attention on how the academic clinical trials environment might be improved.

## **BIOSIMILARS**

### **Q11. DO YOU HAVE ANY COMMENTS ON THE ABOVE?**

The consultation document rightly refers to the risk that biosimilars may not follow the reference product in producing paediatric formulations. Attention should therefore be provided within the Commission's review of the paediatric regulation as to how this matter should be addressed. A distinct system of incentives and obligations may be required.

#### **PUMA – PAEDIATRIC USE MARKETING AUTHORISATION**

**Q12. 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 was designed to address an important problem in paediatric medicines development, and does appear to have at least spurred some activity in this direction. The evidence would suggest of course that more might be done. Furthermore, any improvement to PUMA or other initiative should take place in a context of considering the prevailing approach towards off label use as well. Following from this the consultation document states: “These are complex factors that can hardly be addressed at EU level.” EAHP disagrees. The European Commission frequently plays a vital facilitating role in bringing Member State Governments and others to discuss and advance resolution to complex pan-national challenges. We urge the Commission to do so in respect to the question of encouraging paediatric research for off-patent medicines.

As a further remark upon the question, EAHP notes that since the introduction of the PUMA in 2011 several off-patent medicines for pediatric use have been authorized as orphan drugs: Bronchitol (2012), Defitelio (2013), Granupas (2014), Kolbam (2014), Orphacol (2013), Procysbi (2013), Raxone (2015), Tobi (2011), Votubia (2011) and Xaluprine (2012). This is much more than only three PUMAs in the same period.

#### **SCIENTIFICALLY VALID AND ETHICALLY SOUND CLINICAL TRIALS WITH CHILDREN**

**Q13 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?**

The consultation document states: “so far the exact impact on the number of paediatric trials and study participants is difficult to quantify due to some shortcomings in the available databases with regard to mandatory data.”

Addressing this issue should be one of the priorities of the Commission’s review of the Paediatric Regulation.



In respect to addressing recruitment difficulties for paediatric trials, it must be hoped that the developing European Reference Networks can assist this issue. The Commission's review of the Paediatric Regulation should be informed by any unmet regulatory needs being experienced by the pioneer centres in this programme (e.g. data sharing etc). Such reference networks have a great theoretical potential to tackle common problems in paediatric medicines research such as availability of centres to conduct phase 1 clinical trials for paediatric medicine. It is vital that all barriers to Reference Network success are identified and tackled therefore. Once more, this emphasises the need for a holistic review of the paediatric medicines development environment, and the opportunities for improving EU added value action. Paediatric medicine development in Europe is dependent on more than the 2007 Regulation, and many other outside factors interact with its operational success.

Thinking to the future too, the Commission's review of the Paediatric Medicines regulation should also take account of emerging research trend such as the growing importance of Patient Reported Outcomes. It is perhaps self-evident that in the case of children, arrangements for this require some tailoring and could benefit from European coordination in this regard.

Finally, the 2014 clinical trials regulation promises much in respect to improving the transparency of clinical trial results, a very welcome boost for all involved in medicines development. However it is vital not only that the Regulation delivers on its promise of transparency (for there remain those in active opposition to such developments), but that a means is also found to tackle the problem of past trials that remain unpublished. This is a needless waste of research effort, and the need for retrospective legislation to address the issue should not be considered off-the-table.

#### **THE QUESTION OF FINANCIAL SUSTAINABILITY**

**Q14 DO YOU HAVE ANY VIEWS ON THE ABOVE AND THE FACT THAT THE PAEDIATRIC INVESTIGATION PLAN PROCESS IS CURRENTLY EXEMPT FROM THE FEE SYSTEM**

Given the high unmet need in respect to medicines development for children it is justifiable that the fees charged by EMA for processes for developing adult medicine should help to subsidise free assessment of PIPs.

## POSITIVE IMPACT ON PAEDIATRIC RESEARCH IN EUROPE

### Q15 HOW DO YOU JUDGE THE EFFECTS OF THE PAEDIATRIC REGULATION ON PAEDIATRIC RESEARCH?

The paediatric regulation has established welcome and solid foundations upon which further might be built.

#### *Opportunities for improvement – The Paediatric Committee*

As an example, the establishment of a Paediatric Committee at the European Medicines Agency is a most welcome development. However there is much that might yet be improved in respect to its operation. Some suggestions are made below:

- Improved compensation for healthcare professional members of the Paediatric Committee

The current expectation that a practicing healthcare professional will give at least 3 days per month of their time, away from their family residence, without equivalent compensation of pay, is unrealistic for recruitment purposes and undermines the good intentions of the Paediatric Regulation to insure the Committee benefits from high value healthcare professional participation.

- A statutorily-mandated annual report by the Paediatric Committee on the status of paediatric medicine development in Europe

This should include recommendations to EMA, the European Commission, National Governments, payers, manufacturers and other stakeholders to help bring about year-on-year measurable improvement in paediatric medicines development. It will underpin continuous improvement of the paediatric medicines development environment in Europe.

#### *Opportunities for improvement – Enpr-EMA*

While EAHP applauds the achievements of Enpr-EMA to establish international cooperation via the WHO and FDA<sup>2</sup>, it would be welcome if global outreach in formalised forms could be further

enhanced in the years ahead, including to large global markets and European near-neighbour countries.

## **EMERGING TRENDS AND THE FUTURE OF PAEDIATRIC MEDICINES**

### **Q16 ARE THERE ANY EMERGING TRENDS THAT MAY HAVE AN IMPACT ON THE DEVELOPMENT OF PAEDIATRIC MEDICINES AND THE RELEVANCE OF THE PAEDIATRIC REGULATION?**

EAHP agrees there is a need to keep any prevalent regulatory regime under continuous review to ensure it is fit for purpose and future-proofed. For this reason, it is suggested that the EMA Paediatric Committee be given a statutory responsibility to provide annual report on the operation of the Regulation, and the health of paediatric medicines development in Europe more generally, including any timely recommendations to law-makers that may arise from this.

More specifically, EAHP identifies Advanced Therapy Medicinal Products (ATMPs), including gene therapy, as a key areas for attention when considering the future of paediatric medicines and treatment development. These areas remain nascent and healthcare professionals and health institutions can always benefit from more understanding of particular needs presented (e.g. storage, handling etc). Equally, payers have challenges too in constructing matching reimbursement systems to these new classes of therapy. There is therefore a potentially beneficial role to be played at the EU level in coordinating such considerations, including as these relate to bringing such treatments into the paediatric environment. Glybera and Strimvelis, both ATMPs with marketing authorisation for children as an orphan medicine, give prospective case studies to learn from.

3D printing in the healthcare environment is also becoming increasingly normalised and merits some regulatory consideration. This includes devices used during surgery in small children.

Regrettably too, EAHP receives anecdotal reports of increasing shortages of paediatric medicines across. Examples have included medicines of life-critical nature such as Cerezyme, Fabrazyme and Pedeia. As a pan-European health threat this merits EU response and we urge the Commission to work with national Governments to increase transparency in the supply chain. Further information is available here: <http://www.eahp.eu/press-room/patients-suffering-medicines-shortages-all-european-countries>

#### **OTHER ISSUES TO BE CONSIDERED**

**Q17 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?**

The scientific environment of medicines development is fast-changing and clearly there is a need for the regulatory environment accompanying it to try as it may to keep pace with that change. For that reason, not only paediatric medicine regulation, but other dominant articles of regulation, such as orphan medicine regulation, and the EU community code relating to medicinal products for human use, should be kept under review for opportunities for their improvement. Annual reports, of the nature suggested by EAHP in this consultation response (e.g. by the EMA Paediatric Committee) could assist in this process and encouraging joined-up thinking more generally to how the medicines development environment in Europe be kept optimal for all patient groups, including children.

We also refer the Commission to a previous response of EAHP on the topic of orphan medicine regulation, in which we set out thoughts for improvement in that area, all of which have a bearing for paediatric medicine too.

Amongst the short suggestions for consideration EAHP made included:

- The potential case for 'orphan devices' or 'humanitarian use devices', that similarly meets unmet need for very defined patient group for whom commercial incentive for development is otherwise problematic. This could be especially beneficial for instance in respect of paediatric cardiovascular diseases, where devices for adults are otherwise used off-label.
- Mechanisms to meet the difficulties reported of high priced orphan products. For example, there may be scope for greater matching of the regulatory regime to emerging health technology assessment processes and Commission facilitation in joint procurement.
- Improved surveillance and monitoring of the outcomes of treatment by medicines given orphan drug authorisation with unsettled benefit-risk profiles at the time of approval e.g. conditional approval. This might be achieved, for example, by improvements to systems of patient registry.
- Potential for improvements to the statutory remit and composition of the EMA orphan medicine committee, and transparency requirements within the original regulation of 2000.

More information here:

[http://ec.europa.eu/health/sites/health/files/files/orphanmp/2015\\_11\\_pc\\_orphanmp/replies/2015\\_11\\_pc\\_orphans\\_eahp.pdf](http://ec.europa.eu/health/sites/health/files/files/orphanmp/2015_11_pc_orphanmp/replies/2015_11_pc_orphans_eahp.pdf)